נובמבר 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : <u>עדכון העלון לרופא של התכשירים</u>

<u>Piqray 50 mg film coated tablets</u>
<u>פיקריי 50 מ"ג טבליות מצופות</u>

<u>Piqray 150 mg film coated tablets</u>
<u>פיקריי 150 מ"ג טבליות מצופות</u>

<u>Piqray 200 mg film coated tablets</u>
<u>פיקריי 200 מ"ג טבליות מצופות</u>

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לרופא של התכשירים שבנדון.
העלון עודכן בנובמבר 2022.

העלון נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על-ידי פניה לבעל הרישום: נוברטיס ישראל בע"מ, תוצרת הארץ 6, ת"ד 7126, תל אביב

התווית התכשיר:

PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CAmutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen

חומר פעיל:

alpelisib 50/150/200 mg
אלפליסיב 50/150/200 מ"ג

Novartis Israel Ltd.
P.O.Box 7126 6 Tozeret Haaretz street, Tel Aviv
Tel: 972-3-9201111 Fax: 972-3-9229331

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להלן העידכונים המהווים מידע בטיחותי בלבד בעלון לרופא:

5.3 Dose Modifications for Adverse Reactions

The recommended dose modifications for adverse reactions (ARs) are listed in Table 1.

Table 1: PIQRAY Dose Reduction Guidelines for Adverse Reactions[1]

PIQRAY Dose Level	Dose and Schedule	Number and Strength of Tablets
Starting dose	300 mg once daily	Two 150 mg tablets
First-dose reduction	250 mg once daily	One 200 mg tablet and one 50 mg tablet
Second-dose reduction	200 mg once daily[2]	One 200 mg tablet

[1]Only one dose reduction is permitted for pancreatitis.
[2]If further dose reduction below 200 mg once daily is required, discontinue PIQRAY.

Tables 2, 3, 4, and 5 summarize recommendations for dose interruption, reduction, or discontinuation of PIQRAY in the management of specific ARs.

Cutaneous Adverse Reactions

If a severe cutaneous adverse reaction (SCAR) is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCAR during PIQRAY treatment *[see Warnings and Precautions (7.2)]*.

Table 2: Dose Modification and Management for Rash and Severe Cutaneous Adverse Reactions (SCARs)
[see Warnings and Precautions (7.1, 7.2)]

Grade[1,2]	Recommendation[3]
Grade 1 (< 10% body surface area (BSA) with active skin toxicity)	No PIQRAY dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine to manage symptoms. If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid. If the etiology is SCAR, permanently discontinue PIQRAY.
Grade 2 (10%-30% BSA with active skin toxicity)	No PIQRAY dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low dose systemic corticosteroid treatment. If rash improves to Grade < 1 within 10 days, systemic corticosteroid may be discontinued. If the etiology is SCAR, permanently discontinue PIQRAY.

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Grade 3 (e.g., severe rash not responsive to medical management) (> 30% BSA with active skin toxicity)	Interrupt PIQRAY. Initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment. If the etiology is SCAR, permanently discontinue PIQRAY. If the etiology is not a SCAR, interrupt dose until improvement~~recovery~~ to Grade ≤ 1, then resume PIQRAY at next lower dose level ~~same dose level for first occurrence of rash, or at next lower dose level in case of second occurrence~~.
Grade 4 (e.g., severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue PIQRAY.
[1]Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. [2]For all grades of rash, consider consultation with a dermatologist. [3]Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on the SOLAR-1 trial.	

Hyperglycemia

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment with PIQRAY, monitor fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. In patients with risk factors for hyperglycemia, monitor fasting glucose more closely and as clinically indicated *[see Warnings and Precautions (7.3)]*.

Table 3: Dose Modification and Management for Hyperglycemia
[see Warnings and Precautions (7.3)]

Fasting Plasma Glucose (FPG)/Fasting Blood Glucose Values[1]	**Recommendation**
Dose modifications and management should only be based on fasting glucose values (FPG or fasting blood glucose).	
Grade 1 Fasting glucose > ULN -160 mg/dL or > ULN -8.9 mmol/L	No PIQRAY dose adjustment required. Initiate or intensify anti-hyperglycemic~~diabetic~~ treatment[2].

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Grade 2 Fasting glucose > 160-250 mg/dL or > 8.9-13.9 mmol/L	No PIQRAY dose adjustment required. Initiate or ~~further~~ intensify anti- hyperglycemic~~diabetic~~ treatment[2]. If fasting glucose does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days under appropriate anti-hyperglycemic~~diabetic~~ treatment[2,3], reduce PIQRAY dose by 1 dose level and follow fasting glucose value specific recommendations.
Grade 3 > 250-500 mg/dL or > 13.9-27.8 mmol/L	Interrupt PIQRAY. Initiate or intensify oral anti- hyperglycemic~~diabetic~~ treatment[2] and consider additional anti- hyperglycemic~~diabetic~~ medications[3] for 1-2 days until hyperglycemia improves, as clinically indicated. : Administer intravenous hydration and consider appropriate treatment (e.g., intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). If fasting glucose decreases to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti- hyperglycemic~~diabetic~~ treatment, resume PIQRAY at 1 lower dose level. If fasting glucose does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti- hyperglycemic~~diabetic~~ treatment, consultation with a physician with expertise in the treatment of hyperglycemia is recommended. If fasting glucose does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days following appropriate anti- hyperglycemic~~diabetic~~ treatment[2,3], permanently discontinue PIQRAY treatment.
Grade 4 > 500 mg/dL or > 27.8 mmol/L	Interrupt PIQRAY. Initiate or intensify appropriate anti- hyperglycemic~~diabetic~~ treatment[2] (administer intravenous hydration and consider appropriate treatment (e.g., intervention for electrolyte/ketoacidosis/hyperosmolar disturbances)), re-check fasting glucose within 24 hours and as clinically indicated. If fasting glucose decreases to ≤ 500 mg/dL or 27.8 mmol/L, follow fasting glucose value specific recommendations for Grade 3. If fasting glucose is confirmed at > 500 mg/dL or 27.8 mmol/L, permanently discontinue PIQRAY treatment.
Abbreviation: ULN, upper limit of normal. [1]FPG/Fasting Blood Glucose/Grade levels reflect hyperglycemia grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. [2]Initiate applicable anti- hyperglycemic~~diabetic~~ medications, including metformin, SGLT2 inhibitors or ~~and~~ insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), and review respective prescribing information for dosing and dose titration recommendations, including local hyperglycemic~~diabetic~~ treatment guidelines. Metformin was recommended in the SOLAR-1 trial with the following guidance: *Initiate metformin 500 mg once daily. Based on tolerability, metformin dose may be increased to 500 mg twice daily, followed by 500 mg with breakfast, and 1000 mg with dinner, followed by further increase to 1000 mg twice daily if needed [see Warnings and Precautions (7.3)].* [3]As recommended in the SOLAR-1 trial, insulin may be used for 1-2 days until hyperglycemia resolves. However, this may not be necessary in the majority of PIQRAY-induced hyperglycemia, given the short half-life of PIQRAY and the expectation of glucose levels normalizing after interruption of PIQRAY.	

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Diarrhea

Table 4: Dose Modification and Management for Diarrhea
[see Warnings and Precautions (7.5)]

Grade[1]	Recommendation
Grade 1	No PIQRAY dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Interrupt PIQRAY dose until improvement to Grade < 1, then resume PIQRAY at the same dose level. If diarrhea recurs at Grade > 2, interrupt PIQRAY dose until improvement to Grade < 1, then resume PIQRAY at the next lower dose level. Initiate or intensify appropriate medical therapy and monitor as clinically indicated ~~Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt PIQRAY dose until recovery to Grade < 1, then resume PIQRAY at same dose level.~~
Grade 3 ~~and 4~~	Interrupt PIQRAY dose until improvement to Grade < 1, then resume PIQRAY at the next lower dose level. Initiate or intensify appropriate medical therapy and monitor as clinically indicated ~~Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt PIQRAY dose until recovery to Grade ≤ 1, then resume PIQRAY at the next lower dose level.~~
Grade 4	Permanently discontinue PIQRAY.

[1]Grading according to CTCAE Version 5.0.

Other Toxicities

Table 5: Dose Modification and Management for Other Toxicities (Excluding Hyperglycemia, Rash and Severe Cutaneous Adverse Reactions, and Diarrhea)

Grade[1]	Recommendation
Grade 1 or 2	No PIQRAY dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt PIQRAY dose until improvement~~recovery~~ to Grade ≤ 1, then resume PIQRAY at the next lower dose level.
Grade 4	Permanently discontinue PIQRAY.

[1]Grading according to CTCAE Version 5.0.
[2]For Grade 2 and 3 pancreatitis, interrupt PIQRAY dose until improvement~~recovery~~ to Grade < 2 and resume at next lower-dose level. Only one dose reduction is permitted. If toxicity reoccurs, permanently discontinue PIQRAY treatment.
[3]For Grade 2 total bilirubin elevation, interrupt PIQRAY dose until improvement~~recovery~~ to Grade ≤ 1 and resume at the same dose if resolved in < 14 days or resume at the next lower dose level if improved~~resolved~~ in > 14 days.

Refer to the Full Prescribing Information of fulvestrant for dose modification guidelines in the event of toxicity and for other relevant safety information.

בברכה,
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