

Risks associated with the use of the product

Healthcare Professionals

Addressing hyperglycemia



Indication

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, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Please see full Summary of Product Characteristics or country-specific Brief Succinct Statement.

This document has been reviewed and approved by The Saudi Food and Drug Authority (SFDA).



Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar nonketotic syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with PIQRAY. Some cases of ketoacidosis with fatal outcome have been reported in the postmarketing setting.¹

- ✓ **PIQRAY is associated with an increased risk of hyperglycemia¹**
- ✓ **The PI3K pathway is involved in glucose metabolism, and hyperglycemia is an expected, on-target effect of PI3K inhibition¹**
- ✓ **Hyperglycemia was generally manageable and reversible²**
 - In the phase 3 trial (SOLAR-1), hyperglycemia was reported in 66.9% of patients treated with PIQRAY. Grade 3 and grade 4 hyperglycemia were reported in 33.8% and 4.6% of patients, respectively¹
 - In patients with grade ≥ 2 hyperglycemia with at least 1 grade improvement (n=155), median time to improvement from the first event was 8 days (range: 8-10 days)¹
 - Of the patients with elevated FPG who continued fulvestrant treatment after discontinuing PIQRAY (n=58), 98% (n=57) had FPG levels that returned to baseline (normal)¹
- ✓ **All patients should be tested for fasting plasma glucose (FPG) and HbA1c and the patient's level of blood glucose should be optimized¹**
- ✓ **Patients at higher risk (diabetic, prediabetic, FPG >250 mg/dL, BMI ≥ 30 , or age ≥ 75 years) need consultation with a health care professional or diabetologist experienced in the treatment of hyperglycemia¹**
- ✓ **Counsel patients about the risk of hyperglycemia, need for lifestyle changes according to local guidelines, signs and symptoms of hyperglycemia, and the importance of immediately contacting a health care professional if symptoms occur¹**
 - Signs and symptoms include excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss, difficulty breathing, headache, nausea, and vomiting¹

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin.



- ✓ **Please note there are different monitoring schedules for patients with and without risk factors**

Monitoring guidance for all patients treated with PIQRAY

Fasting Glucose (FG)

- ✓ **Monitor FG at weeks 1, 2, 4, 6, and 8 after treatment start and monthly thereafter¹**

Month 1				Month 2			
Week	Week	Week	Week	Week	Week	Week	Week
1	2	3	4	5	6	7	8

Monitoring week

- ✓ **Monitor or self-monitor* fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment¹**

HbA1c monitoring

- ✓ **Monitor after 4 weeks of treatment and every 3 months thereafter¹**

Month 1				Month 4			Month 7		
Week	Week	Week	Week	Week	Week	Week	Week	Week	
1	2	3	4	2	3	4	2	3	

Monitoring week

Monitoring guidance for patients with diabetes or prediabetes, BMI ≥ 30 , or age ≥ 75 years treated with PIQRAY

Fasting Glucose (FG)

- ✓ **Please refer to above section “Monitoring guidance for all patients treated with PIQRAY”¹**
- ✓ **Monitor or self-monitor* fasting glucose daily for the first 2 weeks of treatment.**
- ✓ **Continue to monitor fasting glucose as frequently as needed to manage hyperglycemia¹**

*All glucose monitoring should be performed at the physicians' discretion as clinically indicated.

HbA1c

- ✓ **Please refer to above section “Monitoring guidance for all patients treated with PIQRAY”¹**



Monitoring and PIQRAY dose adjustment, if hyperglycemia occurs

✓ In case of hyperglycemia, follow the hyperglycemia-related PIQRAY dose modification and management table

✓ Dose modification and management should only be based on fasting glucose (plasma or blood) values

Fasting glucose values ^{*a}	Initial dose modification	Medical management recommendations	Monitoring and PIQRAY dose adjustment
>ULN-160 mg/dL or >ULN-8.9 mmol/L	No PIQRAY dose adjustment required	Initiate or intensify oral antidiabetic treatment ^b	
>160-250 mg/dL or >8.9-13.9 mmol/L	No PIQRAY dose adjustment required	Initiate or intensify oral antidiabetic treatment ^b	<p>If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days with appropriate oral antidiabetic treatment^a: → Reduce PIQRAY dose by 1 dose level and follow FG value-specific recommendations</p>
>250-500 mg/dL or >13.9-27.8 mmol/L	Interrupt PIQRAY	<p> Initiate or intensify oral antidiabetic treatment^b and consider additional antidiabetic medicinal products such as insulin^b for 1-2 days until hyperglycemia resolves, as clinically indicated</p> <p> Administer intravenous hydration and consider appropriate treatment (eg, intervention for electrolyte, ketoacidosis, or hyperosmolar disturbances)</p>	<p>If FG decreases to ≤160 mg/dL or 8.9 mmol/L within 3-5 days under appropriate antidiabetic treatment: → Resume PIQRAY at next lower dose level</p> <p>If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 3-5 days under appropriate antidiabetic treatment: → Consultation with a health care professional with expertise in the treatment of hyperglycemia is recommended</p> <p>If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days following appropriate antidiabetic treatment^b: → Permanently discontinue PIQRAY treatment</p>
>500 mg/dL or ≥27.8 mmol/L	Interrupt PIQRAY	<p> Initiate or intensify appropriate antidiabetic treatment^b</p> <p> Administer intravenous hydration and consider appropriate treatment (eg, intervention for electrolyte, ketoacidosis, or hyperosmolar disturbances)</p> <p> Re-check FG within 24 hours and as clinically indicated</p>	<p>If FG decreases to ≤500 mg/dL or ≤27.8 mmol/L: → Follow FG value-specific recommendations for <500 mg/dL</p> <p>If FG is confirmed at >500 mg/dL or ≥27.8 mmol/L after 24 hours: → Permanently discontinue PIQRAY treatment</p>

CTCAE, Common Terminology Criteria for Adverse Events; FG, fasting glucose; ULN, upper limit of normal.
^aFG levels reflect hyperglycemia grading according to CTCAE Version 4.03.

^aApplicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors, or insulin sensitizers (such as thiazolidiones or dipeptidyl peptidase-4 [DPP-4] inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines. **See next page for metformin recommendations from SOLAR-1.**

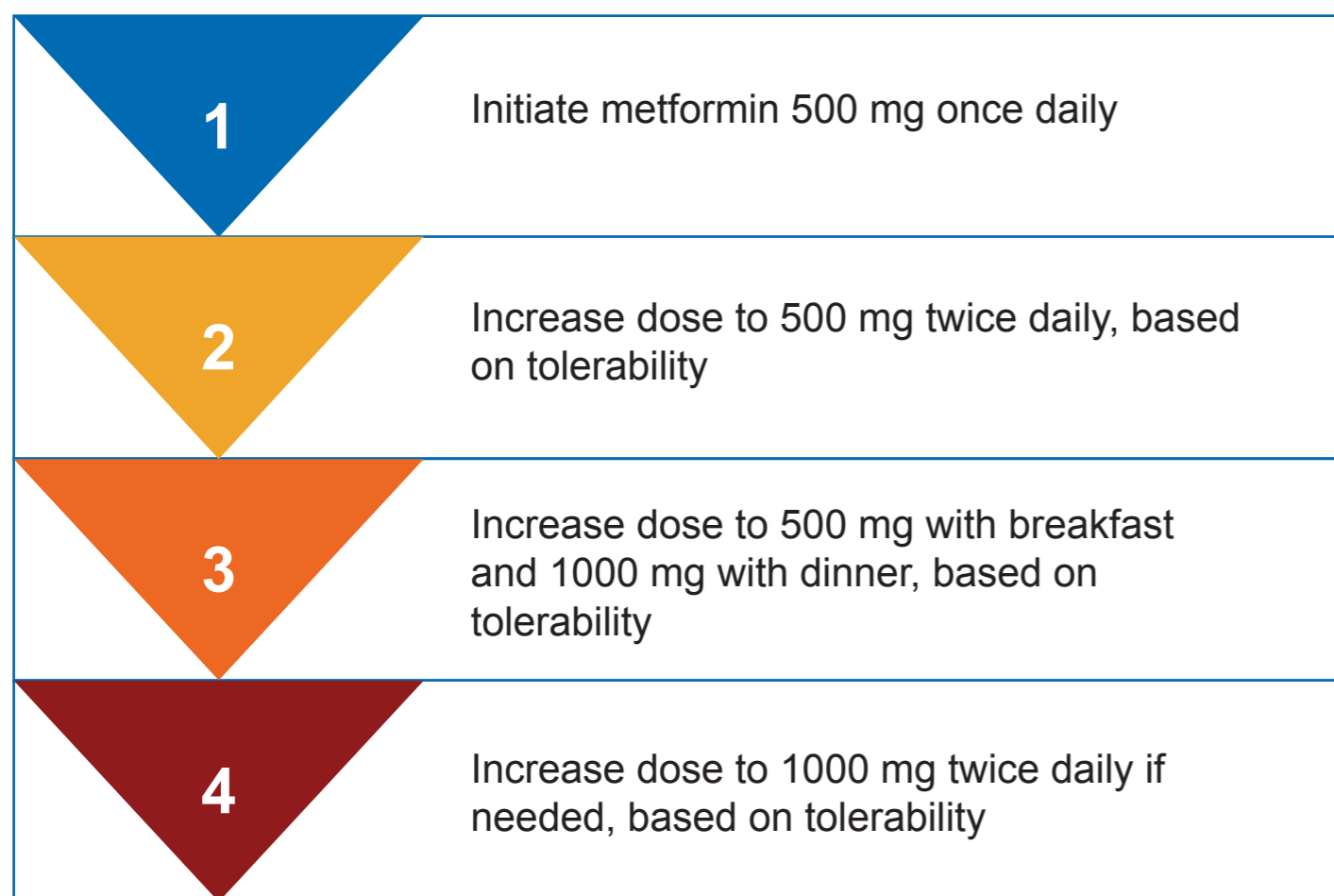
^bAs recommended in the SOLAR-1 study, insulin may be used for 1-2 days until hyperglycemia resolves. However, this may not be necessary in the majority of cases of PIQRAY-induced hyperglycemia, given the short half-life of PIQRAY and the expectation that glucose levels will normalize following interruption of PIQRAY.



Management recommendations if hyperglycemia occurs

- ✓ Applicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors, or insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 [DPP-4] inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines
- ✓ When initiating antidiabetic treatment, consideration should be taken with regard to possible drug-drug interactions¹

In SOLAR-1, metformin was recommended with the following guidance if hyperglycemia occurred¹



Other insulin sensitizers such as thiazolidinediones or DPP-4 inhibitors can also be used as antidiabetic treatment.

- ✓ During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks¹

Monitoring fasting glucose (plasma or blood) during the first 8 weeks

- ✓ Monitor fasting glucose at least 1x per week¹

Month 1				Month 2			
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Monitoring week							

Monitoring week

Monitoring fasting glucose (plasma or blood) after the first 8 weeks

- ✓ Monitor fasting glucose every 2 weeks and as clinically indicated¹

Month 3				Month 4			
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Monitoring week							

Monitoring week

- ✓ Consider consultation with a health care provider with expertise in the treatment of hyperglycemia¹

Adverse drug reactions

You can report any problem or adverse events or request additional copies of the materials through:
Patient Safety Department Novartis Pharma AG - Saudi Arabia -
 Toll Free Number: 8001240078
 Phone: +966112658100
 Fax: +966112658107
 Email: adverse.events@novartis.com
 Or by online: <https://report.novartis.com/>

Saudi Food and Drug Authority National Pharmacovigilance Center
 Unified Contact Center: 19999
 Email: npc.drug@sfd.gov.sa
 Or by online: <https://ade.sfda.gov.sa>

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 شركة نوفارتيس - السعودية - قسم سلامة المرضى:
 الرقم المجاني: 8001240078
 الهاتف: 00966112658100
 الفاكس: 00966112658107
 الإيميل: adverse.events@novartis.com
 أو عن طريق الإنترنت: <https://www.report.novartis.com/ar>

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 مركز الاتصال الموحد: 19999
 الإيميل: npc.drug@sfd.gov.sa
 أو عن طريق الإنترنت: <https://ade.sfda.gov.sa/>



PIQRAY[®]
(alpelisib) tablets