PIQRAY patient management guide for health care professionals

Addressing hyperglycemia

PIQRAY®
(alpelisib) tablets

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, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

Please see full Summary of Product Characteristics.

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

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Before treatment
with PIQRAY

- **PIQRAY is associated with an increased risk of hyperglycemia[1]**
- **The PI3K pathway is involved in glucose metabolism, and hyperglycemia is an expected, on-target effect of PI3K inhibition[1]**
- **Hyperglycemia was generally manageable and reversible[2]**
  - In the phase 3 trial (SOLAR-1), hyperglycemia was reported in 66% of patients treated with PIQRAY. Grade 3 and grade 4 hyperglycemia were reported in 33% and 3.9% of patients, respectively[2]
  - 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)[2]
  - 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 FPG and HbA1c and the patient's level of blood glucose should be optimized[1]**
- **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 hyperglycemia[1]**
- **The patient's current antihyperglycemic treatment might be affected by the treatment with PIQRAY through interaction with oral antihyperglycemics metabolized by CYP2C9 and CYP2C8 (including, but not limited to, repaglinide, rosiglitazone, glipizide, and tolbutamide)[1]**
- **Counsel All patients starting alpelisib 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 occur[1]**
  - 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 vomiting[1]

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

During treatment
with PIQRAY

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

Monitoring guidance for <u>all patients</u> treated with PIQRAY

FPG

- **Monitor FPG at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter[1]**

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

Fasting glucose (plasma or blood)

- **Monitor or self-monitor* fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment[1]**

HbA1c monitoring

- **Monitor after 4 weeks of treatment and every 3 months thereafter[1]**

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

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

FPG

- **Please refer to above section "Monitoring guidance for <u>all patients</u> treated with PIQRAY"[1]**

Fasting glucose (plasma or blood)

- **Monitor or self-monitor* fasting glucose daily for the first 2 weeks of treatment[1]**
- **Continue to monitor fasting glucose as frequently as needed to manage hyperglycemia[1]**

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

HbA1c

- **Please refer to above section "Monitoring guidance for <u>all patients</u> treated with PIQRAY"[1]**

Monitoring and PIQRAY dose adjustment, if hyperglycemia occurs

- **Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels[1]**
- **In case of hyperglycemia, follow the hyperglycemia-related PIQRAY dose modification and management table**

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

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

[a]Applicable antihyperglycemic medicinal products 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**.
[b]As 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

- **In the SOLAR-1 trial, 87.4% (166/190) of patients with hyperglycemia were managed with antihyperglycemic medication[1]**
  - Most patients (75.8%, 144/190) reported use of metformin as a single agent or in combination with other antihyperglycemic medication* (ie, insulin, dipeptidyl peptidase-4 [DPP-4] inhibitors, SGLT2 inhibitors, and sulfonylureas)[1]

  *The maximum dose of metformin allowed in SOLAR-1 was 2000 mg per day.

- **When initiating antihyperglycemic treatment, consideration should be taken with regard to possible drug-drug interactions[1]**

In SOLAR-1, metformin was recommended with the following guidance if hyperglycemia occurred[1]

1	Initiate metformin 500 mg once daily
2	Increase dose to 500 mg twice daily, based on tolerability
3	Increase dose to 500 mg with breakfast and 1000 mg with dinner, based on tolerability
4	Increase dose to 1000 mg twice daily if needed, based on tolerability

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

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- **During treatment with antihyperglycemic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks[1]**

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

- **Monitor fasting glucose at least 1x per week[1]**

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

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

- **Monitor fasting glucose every 2 weeks and as clinically indicated[1]**

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

- **Consider consultation with a health care provider with expertise in the treatment of hyperglycemia[1]**

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
Fax: +966112057662
Email: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

PIQRAY

Important note: Before prescribing, consult full prescribing information.

Presentation: Film-coated tablets (FCT) containing 50 mg, 150mg and 200mg of alpelisib.

Indications: Piqray is an alpha-specific class I phosphatidylinositol-3-kinase (PIK3CA) inhibitor **indicated** for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine-based regimen.

Dosage and administration:

Adults: The recommended dose of Piqray is 300 mg taken orally, once daily on a continuous basis. Piqray should be taken immediately following food, at approximately same time each day. If a dose of Piqray is missed, it can be taken up to 9 hours after the time it is normally administered. After more than 9 hours, the dose should be skipped for that day. On the next day, Piqray should be taken at its usual time. If patient vomits after taking the Piqray dose, the patient should not take an additional dose on that day, and should resume the usual dosing schedule the next day, at the usual time.

Special populations:

♦*Renal impairment:* Mild or moderate: No dose adjustment is necessary.

♦*Severe:* Caution is recommended.

♦*Hepatic impairment:* Mild, moderate or severe: No dose adjustment is necessary.

♦*Geriatrics (≥65 years):* No dose adjustment is required.

♦*Pediatrics (≤18 years):* Safety and efficacy have not been established.

Contraindications: ♦Patients with hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions:

♦**Hypersensitivity (including anaphylactic reaction):** Serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever or tachycardia were reported in patients treated with Piqray in clinical studies. Piqray should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

♦**Severe cutaneous reactions:** Cases of severe cutaneous reactions, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM) and drug reaction with eosinophilia and systemic symptoms (DRESS) were reported in patients treated with Piqray. Piqray treatment should not be initiated in patients with history of severe cutaneous reactions. Patients should be advised of the signs and symptoms of severe cutaneous reactions. If symptoms or signs of severe cutaneous reactions are present, Piqray should be interrupted until the etiology of the reaction has been determined. A consultation with dermatologist is recommended. If a severe cutaneous reaction is confirmed, Piqray should be permanently discontinued. Piqray should not be reintroduced in patients who have experienced previous severe cutaneous reactions. ♦**Hyperglycemia:** Hyperglycaemia was reported in of patients treated with Piqray in the phase III clinical study. Patients with poor glycemic control may be at a higher risk of developing severe hyperglycaemia and associated complications (e.g. ketoacidosis). Patients should be advised of the signs and symptoms of hyperglycemia. Based on the severity of the hyperglycaemia, Piqray may require treatment interruption, dose reduction, or treatment discontinuation.

♦**Pneumonitis**: Pneumonitis including serious cases of pneumonitis/acute interstitial lung disease have been reported in Piqray treated patients in clinical studies. Patients should be advised to promptly report any new or worsening respiratory symptoms. In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, Piqray treatment should be interrupted immediately and the patient should be evaluated for pneumonitis. A diagnosis of non-infectious pneumonitis should be considered. Piqray should be permanently discontinued in all patients with confirmed pneumonitis.

♦**Diarrhea:**Severe diarrhea, including dehydration and acute kidney injury, occurred in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n = 19) of patients. Among patients with Grade 2 or 3 diarrhea (n = 71), the median time to onset was 46 days (range: 1 to 442 days).

Dose reductions of PIQRAY were required in 6% of patients and 2.8% of patients permanently discontinued PIQRAY due to diarrhea. In the 164 patients that experienced diarrhea, anti-diarrheal medications (e.g., loperamide) were required to manage symptoms in 63% (104/164) of these patients.Based on the severity of the diarrhea, piqray may require dose interruption, reduction, or discontinuation.

Pregnancy, lactation, females and males of reproductive potential:

Pregnancy: It is possible that Piqray can cause fetal harm when administered to a pregnant woman. Piqray should not be used during pregnancy unless the benefits to the mother outweigh the risk to the fetus. If Piqray is used during pregnancy, the patient should be advised of the potential risk to the fetus.

Lactation: Women should not breast-feed during treatment and for a week after the last dose of Piqray.

Females and males of reproductive potential: ♦*Pregnancy testing:* For female patients of reproductive potential, the pregnancy status should be verified, prior to initiating treatment with Piqray. ♦*Contraception:* Sexually active females of reproductive potential (ORP) should use effective contraception and male patients with female partners ORP should use condoms during treatment with Piqray and for 4 days after stopping treatment with Piqray.

Infertility: Based on animal studies, Piqray may impair fertility in females and males of reproductive potential.

Adverse drug reactions:

common (≥10%): diarrhoea, nausea, vomiting, stomatitis, abdominal pain, dyspepsia, fatigue, mucosal inflammation, oedema peripheral, pyrexia, mucosal dryness, urinary tract infection, weight decreased, decreased appetite, headache, dysgeusia, rash, alopecia, pruritus, dry skin, Lymphocyte count decreased ,Hemoglobin decreased,Activated Partial Thromboplastin Time (aPTT) prolonged,Platelet count decreased, Biochemical parameters,Glucose increased, Creatinine increased, Gamma Glutamyl Transferase (GGT) increased , Alanine Aminotransferase (ALT) increased , Lipase increasedm Calcium (corrected) decreasedm,Glucose decreased , Potassium decreased , Albumin decreased, Magnesium decreased

Description of select ADRs and treatment recommendations, where applicable:

♦**Rash:** Topical corticosteroid treatment should be initiated at the first signs of rash and oral corticosteroids should be considered for more moderate to severe rashes. Additionally, antihistamines are recommended to manage symptoms of rash. Oral antihistamines may be initiated prophylactically, at the time of initiation of treatment with Piqray.

♦Gastrointestinal **(GI) toxicity (nausea, diarrhoea, vomiting):** Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury have been reported during treatment with Piqray and resolved with appropriate intervention. Patients should be managed according to local standard of care medical management, including electrolyte monitoring, administration of anti-emetics and antidiarrhoeal medications and/or fluid replacement and electrolyte supplements, as clinically indicated.

Interactions:

♦**BCRP (breast cancer resistance protein) inhibitors:** Caution is advised when co-administering Piqray with a BCRP inhibitor (e.g. eltrombopag, lapatinib, pantoprazole), as inhibition of BCRP may lead to an increase in systemic exposure of Piqray.

♦**CYP3A4 substrates**: Caution is recommended when Piqray is used in combination with CYP3A4 substrates that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib).

♦**CYP2C9 substrates with narrow therapeutic index**: No dose adjustment of Piqray is required. However, in the absence of clinical data, caution is recommended when Piqray is co-administered with drugs that are CYP2C9 substrates with narrow therapeutic window (e.g.warfarin).

♦**CYP2B6 sensitive substrates with narrow therapeutic index**: Sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with Piqray, as may reduce the clinical activity of such drugs. ♦**Hormonal contraceptives:** It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Packs and prices: Country-specific.

Legal classification: Country-specific.

References: **1.** Piqray® (alpelisib) EU Summary of Product Characteristics. Novartis. May 2020. **2.** Data on File. Novartis Pharmaceuticals Corp; 2018.

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