PIQRAY patient management guide for health care professionals

Addressing hyperglycemia

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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 or country-specific Brief Succinct Statement.

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Before treatment
with PIQRAY

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 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 66.9% of patients treated with PIQRAY. Grade 3 and grade 4 hyperglycemia were reported in 33.8% and 4.6% of patients, respectively[1]
  - 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 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]**

- **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 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.

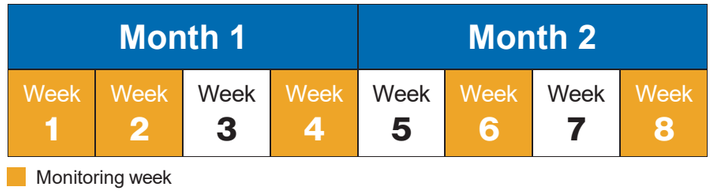
During treatment
with PIQRAY

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

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

Fasting Glucose (FG)

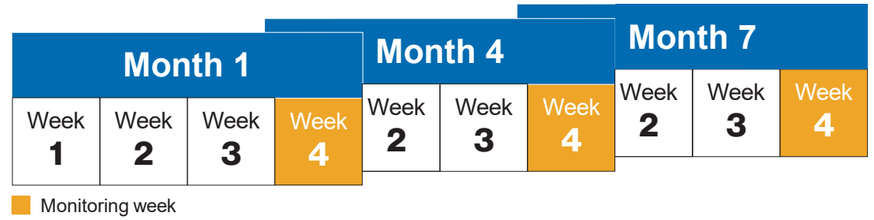
- **Monitor FG at weeks 1, 2, 4, 6, and 8 after treatment start and monthly thereafter[1]**



- **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]**



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

Fasting Glucose (FG)

- Please refer to above section "Monitoring guidance for <u>all patients</u> 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 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

- **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]	**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
>250-500 mg/dL or >13.9-27.8 mmol/L	Interrupt PIQRAY	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 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 antidiabetic 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 antidiabetic 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 antidiabetic treatment[b]:** → Permanently discontinue PIQRAY treatment
>500 mg/dL or ≥27.8 mmol/L	Interrupt PIQRAY	Initiate or intensify appropriate antidiabetic 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 antidiabetic medicinal products, such as metformin, SGLT2 inhibitors, or insulin sensitisers (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.**
[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 antidiabetic medication[1]

- Most patients (75.8%, 144/190) reported use of metformin as a single agent or in combination with other antidiabetic medication* (ie, insulin, DPP-4 inhibitors, SGLT2 inhibitors, and sulfonylureas)[1]

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

When initiating antidiabetic 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 antidiabetic treatment.

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During treatment with antidiabetic 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 week

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

Monitoring week

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

Adverse drug reactions

Suspected Adverse Drug Reactions (side effects) and medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at:
http://www.medicinesauthority.gov.mt/adrportal and sent by post or email to:
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann. SGN 3000. E: postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events associated with the use of Piqray to Novartis Pharma Services Inc., Representative Office, Malta, by phone on +356 21222872, online on www.report.novartis.com or by e-mail at drug_safety.malta@novartis.com.

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For electronic copies of this Educational Material, please refer to the Malta Medicines Authority website - http://www.medicinesauthority.gov.mt/rmm - and download the required material with the latest date.

For more detailed guidance on Piqray please refer to the Summary of Product Characteristics (SmPC) available at:

https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf

This educational material is a part of the conditions of the Marketing Authorisation.

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