PIQRAY patient management guide for health care professionals

▼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/AKT signalling pathway is involved in glucose homestasis 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[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]**
- **The patient's current antidiabetic treatment might be affected by the treatment with PIQRAY through interaction with oral antidiabetics metabolized by CYP2C9 and CYP2C8 (including, but not limited to, repaglinide, rosiglitazone, glipizide, and tolbutamide)[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.

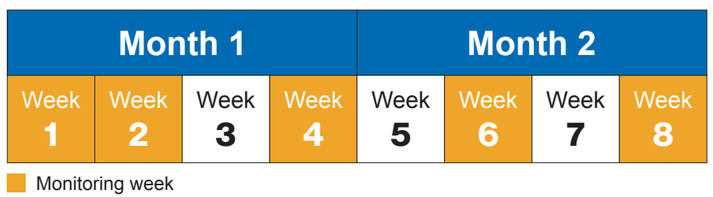
During treatment
with PIQRAY

- **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)

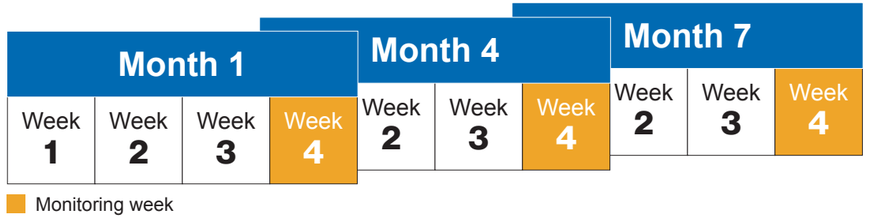
- **Monitor FG at weeks 1, 2, 4, 6, and 8 after treatment start and monthly thereafter[1]**



- **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.

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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) <u>during</u> 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) <u>after</u> 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.

Marketing Authorization Holder: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.
Local Representative: Novartis Pharma Services Inc., Representative Office Malta. Tel No.: +356 21222872
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.

PRODUCT NAME
Piqray® 50mg, 150mg, 200mg film-coated tablets
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. See section 4.8 for how to report adverse reactions. PRESENTATION: Film-coated tablet (tablet) Each film-coated tablet contains 50mg, 150mg or 200mg of alpelisib. INDICATION: Piqray is indicated in combination with fulvestrant for the treatment of postmenopausal women, and me 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. DOSAGE: Patients with HR-positive, HER2-negative advanced breast cancer should be selected for treatment with Piqray based on the presence of a PIK3CA mutation in tumour or plasma specimens, using a validated test. If a mutation is not detected in a plasma specimen, tumour tissue should be tested if available. Piqray is for oral use. Piqray should be co-administered with fulvestrant. The tablets should be swallowed whole. The recommended dose is 300 mg alpelisib (2x 150 mg film-coated tablets) taken once daily on a continuous basi Piqray should be taken immediately after food, at approximately the same time each day. The maximum recommended daily dose of Piqray is 300 mg. Dose modifications may be necessary to improve tolerability – including dose modifications for: adverse drug reactions, hyperglycaemia, ras diarrhoea and other toxicities. In hyperglycaemia: Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should always be considered and is recommended for patients who are pre-diabetic or those with fasting glucose (FG) >250 mg/dl or 13.9 mmol/l, body mass index (BMI) ≥30 or age ≥75 years.
Consultation with a diabetologist or a healthcare professional experienced in the treatment of hyperglycaemia should always take place for patients with diabetes.No dose adjustment is required for elderly patients (above 65 years) and patients with renal (use with caution in severe renal impairment) or hepatic impairment. The safety and efficacy of Piqray in children aged 0-18 have not yet bee established. Piqray treatment should be initiated by a physician experienced in the use of anticancer therapies.
CONTRAINDICATIONS: Hypersensitivity to the active substance or any of the excipients listed in the SmPC. Piqray is not to be used in women who are, or may be pregnant or breast-feeding. WARNINGS/ PRECAUTIONS: Fulvestrant: Efficacy not considered established due to limited data in patients with prior fulvestrant use. Hypersensitivity (including anaphylactic reactions): Serious hypersensitivity reactions (including dyspnoea, flushing, rash, fever or tachycardia) were reported –treatment should be permanently discontinued if serious hypersensitivity reactions occur. Severe cutaneous reactions: Piqray treatment should not be initiated in patients with a history of severe cutaneous reactions. Patients should be advised on signs and symptoms of severe cutaneous reactions. Treatment should be permanently discontinued if severe cutaneous reaction is confirmed and not be re-introduced.
Hyperglycaemia: Severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) or ketoacidosis has been observed in patients treated with Piqray. As hyperglycaemia may occur with a rapid onset after starting treatment, it is recommended to self-monitor frequently in the first 4 weeks and especially within the first 2 weeks of treatment, as clinically indicated (refer to Schedule of fasting glucose monitoring in SmPC). All patients should be instructed on lifestyle changes that may reduce hyperglycaemia (e.g. dietary restrictions and physical activity) and advised of the signs and symptoms of hyperglycaemia. Based on the severity of the hyperglycaemia, Piqray may require dose interruption, reduction or discontinuation. Pneumonitis: Patients should be advised to report promptly 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. Piqray should be permanently discontinued in all patients with confirmed pneumonitis. Diarrhoea: Based on the severity of the diarrhoea, Piqray may require dose interruption, reduction or discontinuation. Patients should be advised to start antidiarrhoeal treatment, increase oral fluids and notify their physician if diarrhoea occurs while taking Piqray. Osteonecrosis of the jaw: Caution should be exercised when Piqray and bisphosphonates or RANK-ligand inhibitors (eg; denosumab) are used either simultaneously or sequentially. Piqray treatment should not be initiated in patients with ongoing osteonecrosis of the jaw from previous or concurrent treatment with bisphosphonates/denosumab. Patients should be advised to promptly report any new or worsening oral symptoms (including: dental mobility, pain or swelling, non-healing of mouth sores, or discharge) during treatment with Piqray. Sodium content: Piqray contains less than 1mmol sodium (23mg) per film-coated tablet – essentially 'sodium-free'. Effects on ability to drive and use machines: Piqray has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or blurred vision during treatment. INTERACTIONS: Drugs which may increase alpelisib plasma concentrations: Caution and monitoring for toxicity are advised during concomitant treatment with inhibitors of BCRP (e.g. eltrombopag, lapatinib, pantoprazole) required. Drugs which may decrease alpelisib plasma concentrations: acid-reducing agents: Alpelisib can be co-administered with acid reducing agents, provided alpelisib is taken immediately after food. Drugs whose plasma concentration may be altered by alpelisib: CYP3A4: no dose adjustment required when co-administering Piqray with CYP3A4 substrates but caution is recommended with CYP3A4 substrates (e.g.everolimus, midazolam) that also possess an additional time-dependent inhibition or induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib). CYP2C9 substrates and CYP2B6 sensitive substrates with narrow therapeutic index: caution recommended. Substances that are substrates of transporters: Piqray has a potential to inhibit activities of OAT3 drug transporters and intestinal BCRP and P-gp. Piqray should be used with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index because Piqray may increase the systemic exposure of these substrates.
FERTILITY, PREGNANCY AND LACTATION: Women of childbearing potential/contraception in males and females: in females of reproductive potential who take Piqray, effective contraception should be used while taking Piqray and for at least 1 week after stopping treatment with Piqray. Male patients with sexual partners who are pregnant, possibly pregnant or who could become pregnant should use condoms during sexual intercourse while taking Piqray and for at least 1 week after stopping treatment with Piqray. Pregnancy: Piqray is not indicated and is not to be used in women who are, or may be, pregnant. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Piqray. Breast-feeding: Because of the potential for serious adverse reactions in the breast-fed infant, it is recommended that women should not breast-feed during treatment and for at least 1 week after the last dose of Piqray. Fertility: Based on repeated dose toxicity studies in animals, alpelisib may impair fertility in males and females of reproductive potential. ADVERSE REACTIONS: Very Common (≥1/10): urinary tract infections, anaemia, lymphocyte count decreased, platelet count decreased, glucose plasma increased or decreased, decreased apetite, hypokalaemia, hypocalcaemia, magnesium decreased, headache, dysgeusia, diarrhoea, nausea, stomatitis, vomiting, abdominal pain, dyspepsia, rash, alopecia, pruritis, dry skin, fatigue, mucosal inflammation, oedema peripheral, pyrexia, mucosal dryness, weight decreased, blood creatinine increased, gamma-glutamyltransferase increased, alanine aminotransferase increased, lipase increased, activated partial thromboplastin time (aPTT) prolonged, albumin decreased. Common(≥1/100 to <1/10): Hypersensitivity, dehydration, insomnia, vision blurred, dry eye, hypertension, lymphoedema, pneumonitis, toothache, gingivitis, gingival pain, cheilitis, erythema, dermatitis, plamar-plantar erythrodysaesthesia syndrome, erythema multiforme, muscle spasms, myalgia, osteonecrosis of jaw, acute kidney injury, oedema, glycosylated haemoglobin increased. LEGAL CATEGORY: POM PACK SIZES: Piqray 50mg and 200mg film-coated tablets: pack containing 56 film-coated tablets (28 of 50 mg and 28 of 200 mg). Piqray 150mg film-coated tablets: pack containing 56 film-coated tablets. Piqray 200mg: pack containing 28 film-coated tablets. MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. MARKETING AUTHORISATION NUMBERS: EU/1/20/1455/001-009. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872. 2021-MT-PIQ-21-MAY-2021

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

References: 1. Piqray® (alpelisib) EU Summary of Product Characteristics. Novartis; May 2021. 2. Data on File. Novartis Pharmaceuticals Corp; 2018.

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