For adults with HR+/HER2-, PIK3CA-mutated, advanced or metastatic breast cancer (aBC or mBC), in combination with fulvestrant following progression on or after an endocrine-based regimen

Plan, monitor, and manage your patient on PIQRAY

Take a proactive approach to patient management

Using this brochure

This brochure is designed to provide guidance on dose modifications and management of selected adverse reactions (ARs). It does not cover all ARs associated with PIQRAY. The management strategies presented here do not constitute medical advice and are not intended to take the place of your own clinical judgment based on each patient's particular presentation. Please refer to the full Prescribing Information for fulvestrant for dose modification guidelines and for relevant safety information.

PIQRAY® (alpelisib) tablets
50 mg · 150 mg · 200 mg

The first therapy specifically for aBC patients with a PIK3CA mutation

Content is consistent with the Oncology Nursing Society Standards and Guidelines. The ONS Seal of Approval does not constitute medical advice, and does not imply product endorsement by ONS. Health care providers should exercise their own independent medical judgment. Website content or other resources referenced in these materials have not been reviewed for the ONS Seal of Approval.

Indication

PIQRAY® (alpelisib) tablets is indicated in combination with fulvestrant for the treatment of adults 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.

Important Safety Information

PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components.

Severe Hypersensitivity: Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms, including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of grade 3 and 4 hypersensitivity reactions was 0.7%. Angioedema has been reported in the postmarketing setting in patients treated with PIQRAY. Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

Patients with a PIK3CA mutation face a poor prognosis[1]

~40% of **HR+/HER2- aBC** patients have a **PIK3CA mutation** and can have aggressive disease, endocrine resistance, and/or shorter mPFS[2-5]

Important Safety Information (cont)

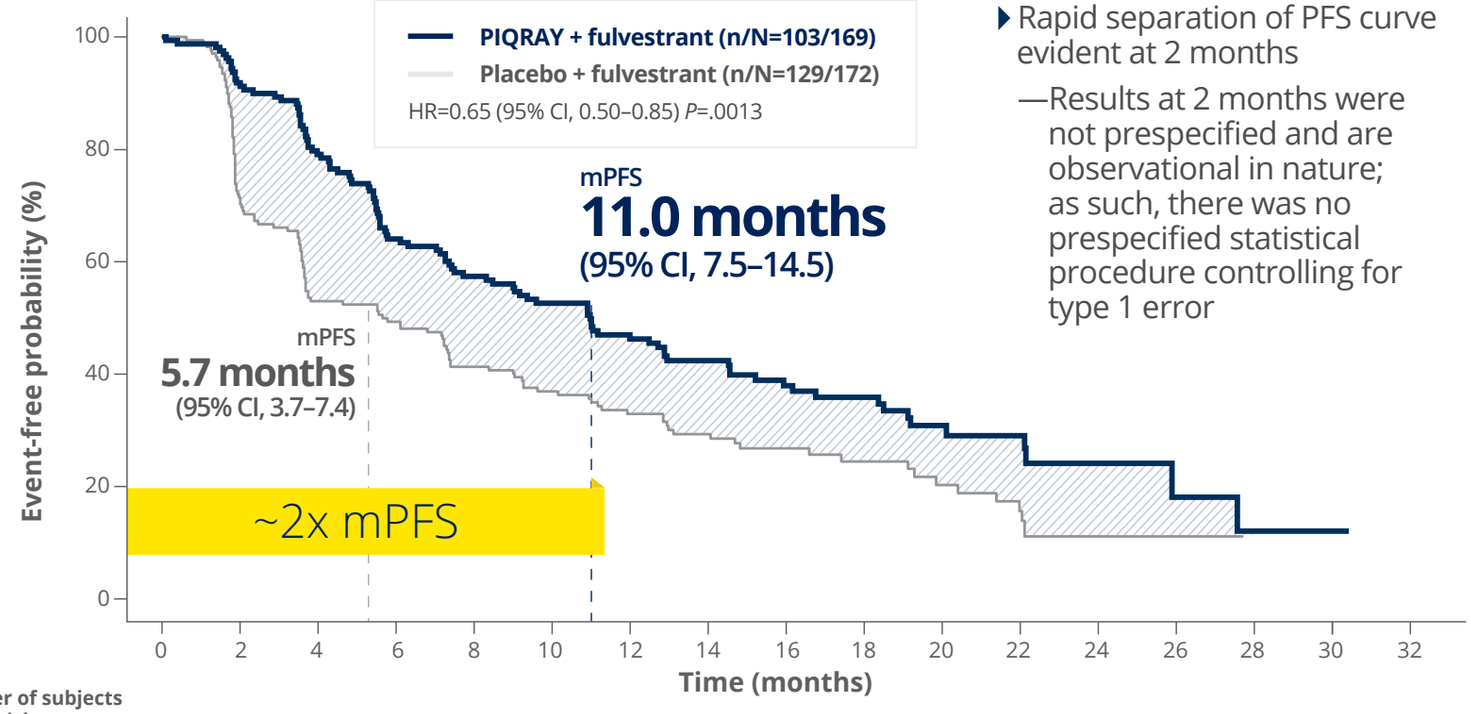
Severe Cutaneous Adverse Reactions (SCARs): SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY. In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of patients, respectively. DRESS was reported in patients in the postmarketing setting. If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

PIQRAY + fulvestrant nearly doubled mPFS in patients with a PIK3CA driver mutation[6]

PFS[6]



- Rapid separation of PFS curve evident at 2 months
  - —Results at 2 months were not prespecified and are observational in nature; as such, there was no prespecified statistical procedure controlling for type 1 error

Number of subjects still at risk:

PIQRAY + fulvestrant	**169**	**145**	**123**	**97**	**85**	**75**	**62**	**50**	**39**	**30**	**17**	**14**	**5**	**3**	**1**	**1**	**0**
Placebo + fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

- At the prespecified final OS analysis, there was no significant difference in OS between the PIQRAY + fulvestrant arm and the placebo + fulvestrant arm (HR=0.86; 95% CI, 0.64-1.15)

mPFS in a post hoc analysis of SOLAR-1

Long-term PFS in a subgroup of patients with a PIK3CA mutation who had reached ≥18 months in a post hoc analysis of SOLAR-1 (non-prespecified)[7]

Observed in **30.2% of patients** treated with PIQRAY + fulvestrant (n/N=51/169)

An **mPFS of 25.6 months** (95% CI, 22.1-29.7) was observed in **22% of patients** treated with placebo + fulvestrant (n/N=38/172).

Results are observational in nature; as such, there was no prespecified statistical procedure controlling for type 1 error.

SOLAR-1 (N=572) is a double-blind, placebo-controlled, multicenter phase 3 study in men and postmenopausal women with HR+/HER2- aBC or mBC with or without a PIK3CA mutation whose disease had progressed or recurred on or after AI-based treatment. In the PIK3CA mutation cohort (n=341), patients were randomized 1:1 to receive PIQRAY 300-mg tablets orally once daily + fulvestrant 500 mg IM (n=169)* or placebo + fulvestrant 500 mg IM (n=172).* The primary endpoint was PFS in patients with a PIK3CA mutation by investigator assessment per RECIST v1.1.[2,6]

*Fulvestrant given on day 1 and day 15 of the first 28-day cycle, then on day 1 of subsequent 28-day cycles.

AI, aromatase inhibitor; IM, intramuscularly; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival.

Important Safety Information (cont)

Severe Cutaneous Adverse Reactions (SCARs) (cont): If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCARs during PIQRAY treatment. If a SCAR is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment.

Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

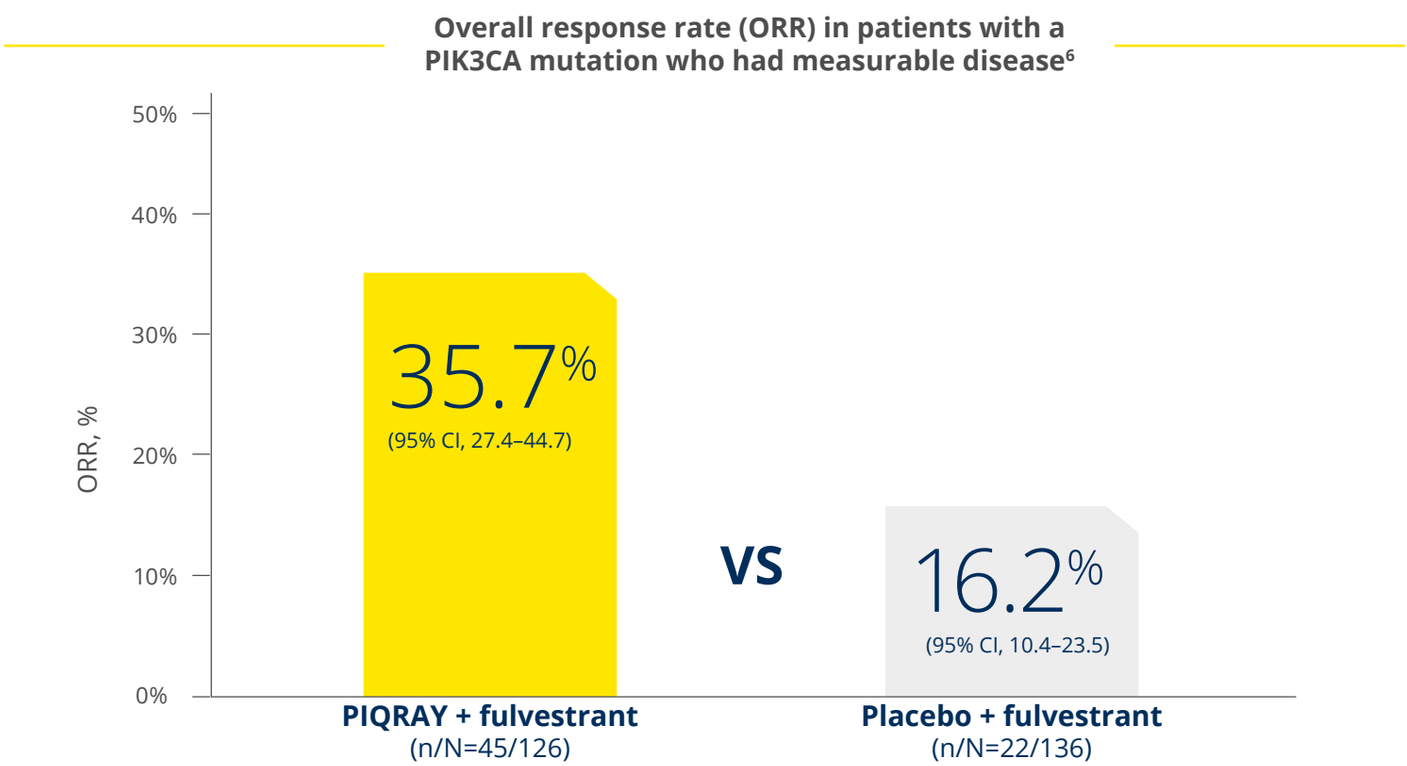
Hyperglycemia: Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis has occurred in patients treated with PIQRAY. Fatal cases of ketoacidosis have occurred in the postmarketing setting.

Please see additional Important Safety Information throughout and on pages 19-20.

Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

PIQRAY + fulvestrant more than doubled the response rate in patients with a PIK3CA driver mutation[6]



ORR was defined as the percentage of subjects with confirmed complete response or partial response. Measurable disease was defined as the presence of at least one measurable nodal or non-nodal lesion as per RECIST v1.1 criteria.

Test for PIK3CA mutations at mBC diagnosis to inform an up-front treatment plan.* Information on FDA-approved tests for the detection of PIK3CA mutations in breast cancer is available at **www.fda.gov/CompanionDiagnostics**

*Following progression on or after an endocrine-based regimen.

Important Safety Information (cont)

Hyperglycemia (cont): Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG >250-500 mg/dL) and grade 4 (FPG >500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY.

Among the patients who experienced Grade ≥ 2 (FPG 160 to 250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range, 5 to 517 days).

In the 187 patients with hyperglycemia, 87% (163/187) were managed with anti-hyperglycemic medication, and 76% (142/187) reported use of metformin as single agent or in combination with other anti-hyperglycemic medication [ie, insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas]. In patients with Grade ≥ 2 hyperglycemia with at least 1 grade improvement (n = 153), median time to improvement from the first event was 8 days (range, 2 to 65 days).

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Safety profile

- Serious ARs associated with PIQRAY include severe hypersensitivity, severe cutaneous adverse reactions (SCARs), hyperglycemia, pneumonitis, diarrhea or colitis, and embryo-fetal toxicity[6]

ARs occurring in >20% of the total population[6]

ARs	PIQRAY + fulvestrant (n=284)		Placebo + fulvestrant (n=287)	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	58	7*	16	0.3*
Nausea	45	2.5*	22	0.3*
Stomatitis[a]	30	2.5*	6	0*
Vomiting	27	0.7*	10	0.3*
General disorders and administration site conditions				
Fatigue[b]	42	5*	29	1*
Investigations				
Weight decreased	27	3.9*	2.1	0*
Metabolism and nutrition disorders				
Decreased appetite	36	0.7*	10	0.3*
Skin and subcutaneous tissue disorders				
Rash[c]	52	20*	7	0.3*
Alopecia	20	0	2.4	0

*No grade 4 ARs were reported.
[a]Including stomatitis, aphthous ulcer, mouth ulceration.
[b]Including fatigue, asthenia.
[c]Including rash, rash maculopapular, rash macular, rash generalized, rash papular, rash pruritic.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Safety profile

Laboratory abnormalities occurring in >30% of the total population[6]

Laboratory abnormality	PIQRAY + fulvestrant (n=284)		Placebo + fulvestrant (n=287)	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
Hematological parameters				
Lymphocyte count decreased	52	8	40	4.5†
Hemoglobin decreased	42	4.2†	29	1†
Biochemical parameters				
Glucose increased[a]	79	39	34	1
Creatinine increased	67	2.8†	25	0.7†
Gamma-glutamyl transferase (GGT) increased	52	11	44	10
Alanine aminotransferase (ALT) increased	44	3.5	34	2.4†
Lipase increased	42	7	25	6

- Glucose increase, including hyperglycemia, is an expected, on-target effect of PI3K inhibition[6,9]
  —Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY[6]
- Among patients treated with PIQRAY and fulvestrant, 5% permanently discontinued both therapies and 21% permanently discontinued PIQRAY alone due to ARs[6]
- Dose reductions due to ARs occurred in 55% of patients receiving PIQRAY and fulvestrant[6]
  —The most common ARs leading to a dose reduction of PIQRAY were hyperglycemia (29% of patients), rash (9%), diarrhea (6%), stomatitis (4%), and mucosal inflammation (2%)

AR, adverse reaction.
†No grade 4 laboratory abnormalities were reported.
[a]Glucose increase is an expected laboratory abnormality of PI3K inhibition. Hyperglycemia, a laboratory-related AR, was reported in 65% of patients treated with PIQRAY (grade 3=33%; grade 4=3.9%).

The most common ARs leading to discontinuation of PIQRAY + fulvestrant were:
Hyperglycemia (6% of patients) | Rash (4%) | Diarrhea (3%) | Fatigue (3%)

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Before treatment with PIQRAY

Antihistamines administered prior to rash onset may decrease the incidence and severity of rash, based on SOLAR-1[6]

- A subgroup of 86 patients receiving PIQRAY + fulvestrant received prophylaxis, including antihistamines (69.8%), such as cetirizine, prior to onset of rash[6,10,11]
- In these patients, rash was reported less frequently than in the overall population, as shown in the table below

	Patients receiving prophylactic treatment prior to onset of rash (n=86)	Overall population (N=284)
All grades rash	27%	54%
Grade 3 rash	12%	20%
Rash leading to permanent discontinuation of PIQRAY	3.5%	4.2%

Novartis offers a PIQRAY Patient Starter Kit, which includes an antihistamine sample

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

During treatment with PIQRAY

Advise patients of signs and symptoms of SCARs and to immediately contact their health care provider should they occur[6]

- Signs and symptoms include a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy

Monitor for different forms of rash

- Rash may present in different forms, including rash, rash maculopapular, rash macular, rash generalized, rash papular, and rash pruritic[6]
- Maculopapular rash—flat, red area covered with small confluent bumps—was reported as one of the most common types of rash[3]
- Examples of maculopapular rash (photos are not from SOLAR-1 trial)[12]:

Images provided by Prof. Dr. Siegfried Segaert (University Hospital Leuven, Leuven, Belgium).

SCARs in SOLAR-1 and postmarketing setting[6]

- In SOLAR-1, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 0.4% and 1.1% of patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) was reported in the postmarketing setting

Rash in SOLAR-1[6]

- 52% of patients experienced all-grade rash during treatment with PIQRAY + fulvestrant
  —Most events were mild to moderate (grade 1 or 2)
  —20% of patients reported grade 3; no grade 4 reported

Median time to first onset of grade 2 or 3 rash[3,6]

12 days (range: 2-220 days)

92%
(141/153)

of patients who experienced rash had resolution of rash[6]

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

If severe cutaneous adverse reactions **(SCARs) or rash occurs**

If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCARs during PIQRAY treatment[6]

Dose modifications and management for rash and SCARs[6]

Assess grade*†	Initial dose modification	Administer medical management‡	Monitor and implement as clinically appropriate
Grade 1 (<10% body surface area [BSA] with active skin toxicity)	No PIQRAY dose adjustment If the etiology is SCAR, permanently discontinue PIQRAY	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
Grade 2 (10%-30% BSA with active skin toxicity)	No PIQRAY dose adjustment If the etiology is SCAR, permanently discontinue PIQRAY	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
Grade 3 (eg, severe rash not responsive to medical management) (>30% BSA with active skin toxicity)	If the etiology is not SCAR, interrupt PIQRAY If the etiology is SCAR, permanently discontinue PIQRAY	Initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment	If the etiology is not SCAR: Interrupt dose until improvement to grade ≤1, then resume PIQRAY at next lower dose level
Grade 4 (eg, severe bullous, blistering, or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue PIQRAY		

*Grading according to CTCAE version 5.0.
†For all grades of rash, consider consultation with a dermatologist.
‡Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on SOLAR-1.
[a]The management plan of each patient should be based on the individual benefit/risk assessment.

Examples of medication used to manage rash in SOLAR-1[11a]

Topical corticosteroids
- Triamcinolone 3x-4x daily
- Betamethasone 3x-4x daily

Oral antihistamines
- Diphenhydramine 25-50 mg 3x daily
- Hydroxyzine 25 mg 3x-4x daily
- Fexofenadine 180 mg daily or 60 mg 3x daily
- Cetirizine

Low-dose oral corticosteroids
- Prednisone 20-40 mg daily or equivalent

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Before treatment with PIQRAY

Assess fasting plasma glucose (FPG) and HbA1c[6]

Optimize blood glucose[6]

- In SOLAR-1, patients with controlled type 2 diabetes and prediabetes were included if they had an FPG ≤140 mg/dL (7.7 mmol/L) and HbA1c ≤6.4% (both criteria had to be met)[3]

Assess patient's past medical history[6]

- The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from SOLAR-1. Patients with a medical history of controlled type 2 diabetes were included
- Patients with a history of diabetes mellitus may require intensified hyperglycemic treatment. Closely monitor patients with diabetes

Have a prescription ready for metformin in the event that your patient experiences hyperglycemia

- 87% of patients (163/187) were managed with antihyperglycemic medication in the SOLAR-1 trial; 76% (142/187) used metformin as a single agent or in combination with other antihyperglycemic medications[6]

Counsel patients that lifestyle changes such as diet modifications (eg, restricting carbohydrates, portion control, nutrient-dense, high-fiber foods) and increased exercise may be recommended as part of hyperglycemia management[6,13]

Consider prescribing a glucometer when starting patients on PIQRAY to begin regular monitoring of fasting glucose at home

- Including a glucometer prescription will ensure that your patients can do the required fasting glucose monitoring on a regular basis, with more frequent monitoring for patients with risk factors for hyperglycemia and at your clinical discretion[6]*

*Risk factors include obesity (BMI ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75. In addition to FPG, HbA1c levels should be monitored. Please refer to the PI for recommended monitoring intervals.

HbA1c, glycosylated hemoglobin.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

During treatment with PIQRAY

Advise patients of signs and symptoms of hyperglycemia and to contact their health care provider immediately should they occur[6]

- Signs and symptoms include excessive thirst, urinating more often than usual or a higher amount of urine than usual, or increased appetite with weight loss

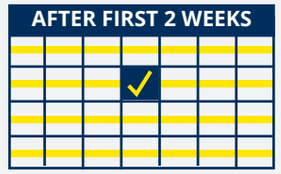
Monitor for hyperglycemia throughout your patient's treatment[6]

- The only laboratory monitoring needed for patients on PIQRAY is for fasting glucose **(FPG or fasting blood glucose)** and HbA1c
- Monitor more frequently for the first few weeks during treatment in patients with risk factors for hyperglycemia such as obesity (BMI ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75
- Self-monitoring with a glucometer may help with reporting of elevated blood sugar[6]

Fasting glucose (FPG or fasting blood glucose)

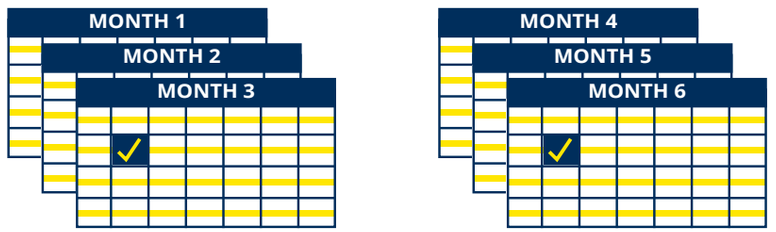
First 2 weeks of treatment:
At least 1x per week

After first 2 weeks of treatment:
At least once every 4 weeks and as clinically indicated



HbA1c

Duration of treatment
Once every 3 months and as clinically indicated



Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Before PIQRAY | **During PIQRAY** | If Hyperglycemia Occurs | If Hyperglycemia Occurs (cont) | Dose Modification
Cutaneous AR | **Hyperglycemia** | Diarrhea | Other Toxicities
Poor Prognosis | Efficacy | Safety | **Patient Management** | Dosing | Important Safety Information | Summary

If hyperglycemia occurs

Adjust monitoring schedule[6]

- Monitor fasting glucose as clinically indicated and **at least 2x per week** until fasting glucose decreases to normal levels

Consider consultation with a health care provider with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes, such as diet modifications and increased exercise, as a part of hyperglycemia management[6]

- Self-monitoring of FPG with a glucometer may help identify elevated blood glucose if hyperglycemia occurs[6]

During treatment with antihyperglycemic medication

First 8 weeks:
Monitor fasting glucose at least 1x per week

After first 8 weeks:
Monitor fasting glucose every 2 weeks and as clinically indicated

In SOLAR-1, metformin was recommended with the following guidance if hyperglycemia occurred[6]

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

Examples of additional antihyperglycemic medication[6,14-22]

SGLT2 inhibitors
- Dapagliflozin 5-10 mg daily
- Canagliflozin 100-300 mg daily before meals
- Empagliflozin 10-25 mg daily

DPP-4 Inhibitors
- Alogliptin 25 mg daily
- Saxagliptin 2.5-5 mg daily
- Linagliptin 5 mg daily
- Sitagliptin 100 mg daily

Thiazolidinediones
- Pioglitazone 15-45 mg daily
- Rosiglitazone 4-8 mg daily

Review respective prescribing information for dosing and dose titration recommendations, including local hyperglycemic treatment guidelines.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

If hyperglycemia occurs

Glucose increase, including hyperglycemia, is an expected, on-target effect of PI3K inhibition[6,9]

65% of patients treated with PIQRAY in SOLAR-1 reported hyperglycemia[6]

- Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis has occurred in patients treated with PIQRAY. Fatal cases of ketoacidosis have occurred in the postmarketing setting
- Grade 3 (FPG >250-500 mg/dL): 33% and Grade 4 (FPG >500 mg/dL): 3.9%
  - —Glucose increase (all grades) was reported in 79% of patients treated with PIQRAY + fulvestrant

In SOLAR-1, hyperglycemia was generally manageable and reversible[6]

87% of patients (163/187) with hyperglycemia were managed with antihyperglycemic medication[6]

- Of the 187 patients experiencing hyperglycemia, 76% (142/187) used metformin as a single agent or in combination with other antihyperglycemic medications*
  - —Examples of antihyperglycemic medications used in combination with metformin include insulin, DPP-4 inhibitors, and sulfonylureas

96% (n=52) of patients with elevated FPG who continued fulvestrant treatment after discontinuing PIQRAY (n=54) had FPG levels that returned to baseline[6]

Median time to first occurrence for grade ≥2 (FPG 160-250 mg/dL) hyperglycemia[6]

15 days (range: 5-517 days)

Median time to improvement from the first event: 8 days (range: 2-65 days) for grade ≥2 hyperglycemia with ≥1 grade improvement (n=153)

DPP-4, dipeptidyl peptidase-4.
*The maximum dose of metformin allowed in SOLAR-1 was 2000 mg/d.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

If hyperglycemia occurs

Dose modifications and management should only be based on fasting glucose values (FPG or fasting blood glucose)[6]

Assess grade[†]	Initial dose modification	Administer medical management	**Monitor and implement** as clinically appropriate
Grade 1 Fasting glucose >ULN-160 mg/dL	No PIQRAY dose adjustment	Initiate or intensify antihyperglycemic treatment[a]	
Grade 2 Fasting glucose >160-250 mg/dL	No PIQRAY dose adjustment	Initiate or intensify antihyperglycemic treatment[a]	**If fasting glucose does not decrease to ≤160 mg/dL within 21 days under appropriate antihyperglycemic treatment[a,b]:** → Reduce dose by 1 level and follow fasting glucose value-specific recommendations
Grade 3 >250-500 mg/dL	Interrupt PIQRAY	Initiate or intensify oral antihyperglycemic treatment[a] and consider additional antihyperglycemic medications[b] for 1-2 days until hyperglycemia improves, as clinically indicated Administer IV hydration and consider appropriate treatment including intervention for electrolyte/ketoacidosis/ hyperosmolar disturbances	**If fasting glucose decreases to ≤160 mg/dL within 3-5 days under appropriate antihyperglycemic treatment:** → Resume at 1 lower dose level **If fasting glucose does not decrease to ≤160 mg/dL within 3-5 days under appropriate antihyperglycemic treatment:** → Consultation with a physician with expertise in the treatment of hyperglycemia is recommended **If fasting glucose does not decrease to ≤160 mg/dL within 21 days following appropriate antihyperglycemic treatment[a,b]:** → Permanently discontinue
Grade 4 >500 mg/dL	Interrupt PIQRAY	Initiate or intensify appropriate antihyperglycemic treatment[a,b] Administer IV hydration and consider appropriate treatment including 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 within 24 hours:** → Follow fasting glucose value-specific recommendations for grade 3 **If fasting glucose is confirmed at >500 mg/dL:** → Permanently discontinue

ULN, upper limit of normal.
[†]FPG/Fasting Blood Glucose/Grade levels reflect hyperglycemia grading according to CTCAE version 4.03.
[a]Initiate applicable antihyperglycemic medications, including metformin, SGLT2 inhibitors, or insulin sensitizers (such as thiazolidinediones, DPP-4 inhibitors), and review respective prescribing information for dosing and dose titration recommendations, including local hyperglycemic treatment guidelines. Metformin was recommended in SOLAR-1 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 a further increase to 1000 mg twice daily if needed.
[b]As recommended in SOLAR-1, 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.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

Management in the event of diarrhea or colitis

In SOLAR-1[6]

- 58% of patients experienced diarrhea during treatment with PIQRAY + fulvestrant
  —7% (n=19) of patients had grade 3 diarrhea
- Colitis has been reported in the postmarketing setting in patients treated with PIQRAY

Median time to onset of grade 2 or 3 diarrhea (n=71): 46 days (range: 1-442 days)

- 63% of patients who experienced diarrhea required antidiarrheal medications (eg, loperamide) to manage symptoms
- Dose reductions of PIQRAY were required in 6% of patients, and 2.8% of patients permanently discontinued PIQRAY due to diarrhea

Monitor patients for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool[6]

- Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs
- For patients with colitis, additional treatment, such as enteric-acting and/or systemic steroids, may be required

Dose modifications and management for diarrhea or colitis[6]

Grade*	Modify dose	Administer medical management and monitor as clinically indicated
Grade 1	No PIQRAY dose adjustment	Initiate appropriate medical therapy and monitor as clinically indicated
Grade 2	Interrupt PIQRAY dose until improvement to grade ≤1, then resume PIQRAY at same dose level. For recurrent 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
Grade 3	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
Grade 4	Permanently discontinue PIQRAY	

*Grading according to CTCAE version 5.0.
[†]For grade 2 and 3 colitis consider additional treatment, such as enteric-acting and/or systemic steroids.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Management in the event of other toxicities

Dose modifications and management for other toxicities[6]

(Excluding hyperglycemia, rash and severe cutaneous adverse reactions, and diarrhea or colitis)

Grade†	Modify dose	Administer medical management and monitor as clinically indicated
Grade 1 or 2	No PIQRAY dose adjustment[a,b]	Initiate appropriate medical therapy and monitor as clinically indicated
Grade 3	Interrupt PIQRAY dose until improvement to grade ≤1, then resume PIQRAY at the next lower dose level	
Grade 4	Permanently discontinue PIQRAY	

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

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Dosing and administration

PIQRAY is given in combination with fulvestrant[6]

PIQRAY
Starting dose: 300 mg daily
(Two 150-mg tablets)

Once-daily continuous oral dosing
Should be swallowed whole and taken with food, at approximately the same time each day*

+

FULVESTRANT
Recommended dose: 500 mg

Administered on days 1, 15, and 29, and once monthly thereafter
Please refer to the full Prescribing Information for fulvestrant

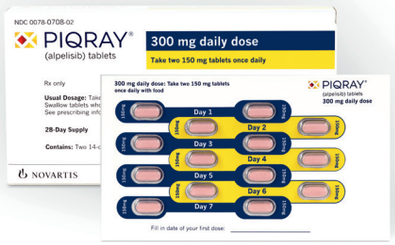
Continue treatment until disease progression or unacceptable toxicity occurs

*Tablets should not be chewed, crushed, or split prior to swallowing. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

PIQRAY may be affected by other drugs, including CYP3A4 inducers and BCRP inhibitors. PIQRAY may have an effect on other drugs, including CYP2C9 substrates

Blister pack is designed to help patients stay on track with treatment[6]

300 mg
(Two 150-mg tablets once daily)

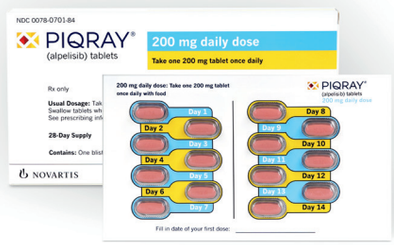


NDC 0078-0708-02

250 mg
(One 200-mg tablet + one 50-mg tablet once daily)

NDC 0078-0715-02

200 mg
(One 200-mg tablet once daily)



NDC 0078-0701-84

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets
50 mg · 150 mg · 200 mg

Dosing and administration

Certain ARs may require dose modifications[6]

Starting dose	First dose reduction	Second dose reduction
300 mg once daily (Two 150-mg tablets)	**250 mg once daily** (One 200-mg tablet + one 50-mg tablet)	**200 mg once daily** (One 200-mg tablet)
		
Not actual size.	Not actual size.	Not actual size.

- Dose interruptions may be required prior to dose reductions. The PIQRAY dose may be reduced in increments of 50 mg† but if further dose reduction below 200 mg/d is required, discontinue PIQRAY
- Dose reductions due to ARs occurred in 55% of patients receiving PIQRAY + fulvestrant
  - —The most common ARs leading to a dose reduction of PIQRAY were hyperglycemia (29% of patients), rash (9%), diarrhea (6%), stomatitis (4%), and mucosal inflammation (2%)
  - —No dose adjustment is recommended for patients with mild to moderate renal impairment (CLcr 30 to <90 mL/min)

†Only one dose reduction is permitted for pancreatitis.

Please refer to the full Prescribing Information for dose interruption, reduction, or discontinuation of PIQRAY in specific ARs. The management plan of each patient should be based on the individual benefit/risk assessment.

Please see additional Important Safety Information throughout and on pages 19-20
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Important Safety Information

Indication

PIQRAY tablets is indicated in combination with fulvestrant for the treatment of adults 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.

Important Safety Information

PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components.

Severe Hypersensitivity: Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of grade 3 and 4 hypersensitivity reactions was 0.7%. Angioedema has been reported in the postmarketing setting in patients treated with PIQRAY. Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

Severe Cutaneous Adverse Reactions (SCARs): SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY. In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of patients, respectively. DRESS was reported in patients in the postmarketing setting. If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCARs during PIQRAY treatment. If a SCAR is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment.

Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

Hyperglycemia: Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis has occurred in patients treated with PIQRAY. Fatal cases of ketoacidosis have occurred in the postmarketing setting.

Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG >250-500 mg/dL) and grade 4 (FPG >500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY.

Among the patients who experienced Grade ≥ 2 (FPG 160 to 250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range, 5 to 517 days).

In the 187 patients with hyperglycemia, 87% (163/187) were managed with anti-hyperglycemic medication, and 76% (142/187) reported use of metformin as single agent or in combination with other anti-hyperglycemic medication [ie, insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas]. In patients with Grade ≥ 2 hyperglycemia with at least 1 grade improvement (n = 153), median time to improvement from the first event was 8 days (range, 2 to 65 days).

In all patients with elevated FPG who continued fulvestrant treatment after discontinuing PIQRAY (n = 54), 96% (n = 52) of patients had FPG levels that returned to baseline.

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment, 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. Monitor fasting glucose more frequently for the first few weeks during treatment in patients with risk factors for hyperglycemia such as obesity (BMI ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75.

Please see additional Important Safety Information throughout and on next page.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets
50 mg · 150 mg · 200 mg

Important Safety Information (cont)

Hyperglycemia (cont): If a patient experiences hyperglycemia after initiating treatment, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a health care practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes.

The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of controlled type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified hyperglycemic treatment. Closely monitor patients with diabetes.

Consider premedication with metformin prior to the initiation of PIQRAY in combination with fulvestrant based on patient risk factors for hyperglycemia, gastrointestinal tolerability, and clinical situation. In the METALLICA study, use of metformin starting 7 days prior to the initiation of PIQRAY appeared to decrease the incidence and severity of hyperglycemia events, but increased the incidence and severity of nausea, vomiting, and diarrhea adverse reactions.

Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients of the signs and symptoms of hyperglycemia (eg, excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss).

Pneumonitis: Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, can occur in patients treated with PIQRAY. Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis. Consider a diagnosis of noninfectious pneumonitis in patients presenting with nonspecific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue PIQRAY in all patients with confirmed pneumonitis. Advise patients to immediately report new or worsening respiratory symptoms.

Diarrhea or Colitis: Severe diarrhea, resulting in dehydration and in some cases in acute kidney injury, can occur 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). In clinical trials, 63% of patients who experienced diarrhea required antidiarrheal medications (eg, loperamide) to manage symptoms. Dose reductions of PIQRAY were required in 6% of patients, and 2.8% of patients permanently discontinued PIQRAY due to diarrhea. Colitis has been reported in the postmarketing setting in patients treated with PIQRAY. Monitor patients for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus, or blood in the stool. Based on the severity of the diarrhea or colitis, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their health care provider if diarrhea occurs while taking PIQRAY. For patients with colitis, additional treatment, such as enteric-acting and/or systemic steroids, may be required.

Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose. Refer to the full Prescribing Information of fulvestrant for pregnancy and contraception information.

The most common adverse reactions (all grades, incidence ≥20%) were diarrhea (58%), rash (52%), nausea (45%), fatigue (42%), decreased appetite (36%), stomatitis (30%), vomiting (27%), weight decreased (27%), and alopecia (20%). The most common grade 3/4 adverse reactions (incidence ≥2%) were rash (20%), diarrhea (7%), fatigue (5%), weight decreased (3.9%), nausea (2.5%), stomatitis (2.5%), and mucosal inflammation (2.1%).

The most common laboratory abnormalities (all grades, incidence ≥20%) were glucose increased (79%), creatinine increased (67%), lymphocyte count decreased (52%), gamma-glutamyl transferase (GGT) increased (52%), alanine aminotransferase (ALT) increased (44%), hemoglobin decreased (42%), lipase increased (42%), calcium decreased (27%), glucose decreased (26%), and activated partial thromboplastin time (aPTT) prolonged (21%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were glucose increased (39%), GGT increased (11%), lymphocyte count decreased (8%), lipase increased (7%), and potassium decreased (6%).

PIQRAY®
(alpelisib) tablets
50 mg · 150 mg · 200 mg

Please click here for full Prescribing Information.

References

References: 1. Mosele F, Stefanovska B, Lusque A, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. *Ann Oncol.* 2020;31(3):377-386. **2.** André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med.* 2019;380(20):1929-1940. **3.** Data on file. Novartis Pharmaceuticals Corp; 2018. **4.** Mollon LE, Anderson EJ, Dean JL, et al. A systematic literature review of the prognostic and predictive value of PIK3CA mutations in HR+/HER2- metastatic breast cancer. *Clin Breast Cancer.* 2020;20(3):e232-e243. **5.** The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature.* 2012;490(7418):61-70. **6.** Piqray. Prescribing information. Novartis Pharmaceuticals Corp. **7.** Data on file. Novartis Pharmaceuticals Corp; 2021. **8.** Ciruelos EM, Rugo HS, Mayer IA, et al. Patient-reported outcomes in patients with PIK3CA-mutated hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer from SOLAR-1. *J Clin Oncol.* Published online March 29, 2021. doi:10.1200/JCO.20.01139 **9.** Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-kinase, growth disorders, and cancer. *N Engl J Med.* 2018;379(21):2052-2062. **10.** Rugo HS, Andre F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. *Ann Oncol*. 2020;31(8):1001-1010. **11.** Data on file. Novartis Pharmaceuticals Corp; 2017. **12.** OncologyPRO. https://oncologypro.esmo.org/Oncology-in-Practice/Palliative-and-Supportive-care/Multikinase-Inhibitor-Related-Skin-Toxicity/Healthcare-Professionals/Symptoms-and-Grading/Skin-Changes/Maculopapular-Rash. Accessed March 18, 2024. **13.** Summary of Revisions: *Standards of Medical Care in Diabetes—2019*. *Diabetes Care*. 2019;42(suppl 1):4S-6S. **14.** Actos [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **15.** Avandia [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline. **16.** Farxiga [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **17.** Invokana [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **18**. Januvia [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc. **19.** Jardiance [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **20.** Nesina [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **21.** Onglyza [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **22.** Tradjenta [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Patient management RoadMAP

Prior to starting your patient's treatment on PIQRAY + fulvestrant, consider these strategies to prepare for potential select adverse reactions (ARs) and help with the start of your patient's treatment.

M — MONITORING FOR HYPERGLYCEMIA

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG) and HbA1c and optimize blood glucose[6]

Consider prescribing a glucometer when starting patients on PIQRAY to begin regular monitoring of FPG at home

- In SOLAR-1, patients with controlled type 2 diabetes and prediabetes were included if they had an FPG ≤140 mg/dL (7.7 mmol/L) and HbA1c ≤6.4% (both criteria had to be met)[3]
- The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of controlled type 2 diabetes were included[6]

A — ANTIHYPERGLYCEMIC MEDICATION (EG, METFORMIN)

Be ready to prescribe metformin or other antihyperglycemic medications

- 87% of patients (163/187) were managed with antihyperglycemic medication in the SOLAR-1 trial; 76% (142/187) used metformin as a single agent or in combination with other antihyperglycemic medications[6]

P — PROPHYLACTIC ANTIHISTAMINES

Monitor for different forms of rash throughout treatment[6]

Antihistamines administered prior to rash onset may decrease the incidence and severity of rash, based on SOLAR-1[6]

- A subgroup of 86 patients receiving PIQRAY + fulvestrant received prophylaxis, including antihistamines (69.8%), such as cetirizine, prior to onset of rash[6,10,11]
- In these patients, rash was reported less frequently than in the overall population, for all grades rash (27% vs 54%), Grade 3 rash (12% vs 20%) and rash leading to permanent discontinuation of PIQRAY (3.5% vs 4.2%). Of the 153 patients who experienced rash, 141 had resolution of the rash[6]

Please refer to the PIQRAY safety profile for additional ARs and the full Prescribing Information for additional monitoring and management guidance.
The management plan of each patient should be based on the individual benefit/risk assessment. The information presented here does not constitute medical advice and is not intended to take the place of your own clinical judgment based on a patient's particular presentation.

Selected Important Safety Information
Serious ARs associated with PIQRAY include severe hypersensitivity, severe cutaneous adverse reactions (SCARs), hyperglycemia, pneumonitis, diarrhea or colitis, and embryo-fetal toxicity.

Most common ARs (incidence >20%) are diarrhea, rash, nausea, fatigue, decreased appetite, stomatitis, vomiting, weight decreased, and alopecia.

Please see additional Important Safety Information throughout and on pages 19-20.
Please click here for full Prescribing Information.

NOVARTIS

PIQRAY® (alpelisib) tablets 50 mg · 150 mg · 200 mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

4/24

422648