Product Monograph

Including Patient Medication Information

PrPIQRAY®

Alpelisib
Tablets
For oral use
50 mg, 150 mg and 200 mg

Antineoplastic Agent

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Recent Major Label Changes

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Health Professional Information

1. Indications

PIQRAY® (alpelisib), in combination with fulvestrant, is indicated for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative, PIK3CA- mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen.

1.1. Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for paediatric use.

1.2. Geriatrics

No overall differences in the efficacy of PIQRAY were observed between patients ≥ 65 years of age compared to younger patients (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

2. Contraindications

PIQRAY is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3. Serious Warnings and Precautions Box

The following serious adverse reactions were reported in patients treated with PIQRAY.

- Hypersensitivity, including anaphylactic reaction (see *7 WARNINGS AND PRECAUTIONS, Immune*)
- Severe cutaneous adverse reactions including Stevens-Johnson Syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms and Erythema Multiforme (see *7 WARNINGS AND PRECAUTIONS, Skin*)
- Hyperglycemia, including hyperglycemic hyperosmolar non-ketotic syndrome and some fatal cases of diabetic ketoacidosis (see *7 WARNING AND PRECAUTIONS, Endocrine and Metabolism*)
- Pneumonitis (see *7 WARNINGS AND PRECAUTIONS, Respiratory*)

4. Dosage and Administration

Treatment with PIQRAY should be initiated by a physician experienced in the use of anticancer therapies.

4.1. Dosing Considerations

Patients with hormone receptor (HR) positive, HER2-negative advanced breast cancer, should be selected for treatment with PIQRAY based on the presence of a PIK3CA mutation using a validated test. There was no treatment benefit demonstrated in breast cancer patients without a PIK3CA mutation, in

the phase III clinical study; therefore, treatment with PIQRAY is not recommended for these patients (see 14 CLINICAL TRIALS).

Correct glucose levels in patients with abnormal glucose levels before initiating PIQRAY, and closely monitor glucose levels to enable early detection and early treatment of hyperglycemia. Premedication with metformin (e.g., 500 mg twice daily on days 1-3, then increased to 1000 mg twice daily based on tolerability), administered 7 days prior to initiation of PIQRAY in combination with fulvestrant, should be considered based on patient risk factors for hyperglycemia and gastrointestinal tolerability (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of PIQRAY is 300 mg (2×150 mg film-coated tablets) taken orally, once daily on a continuous basis. PIQRAY should be taken immediately following food, at approximately the same time each day (see 10 CLINICAL PHARMACOLOGY and 9. DRUG INTERACTIONS).

The maximum recommended daily dose of PIQRAY is 300 mg.

If the 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.

When co-administered with PIQRAY, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29 and every 28 days thereafter. Please refer to the full prescribing information in the fulvestrant Product Monograph.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Dosing modifications may be necessary to improve tolerability.

Dose modifications

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dosing interruption, reduction, and/or discontinuation of PIQRAY. The dosing reduction guidelines for ADRs are listed in Table 4-1. A maximum of 2 dosing reductions are recommended, after which the patient should be discontinued from treatment with PIQRAY (see also 14 CLINICAL TRIALS). Dose reduction should be based on worst preceding toxicity.

In the phase III study, patients who discontinued PIQRAY were to continue taking fulvestrant as per the treating physician's clinical judgment.

Table 4-1 Recommended dose reduction guidelines for adverse drug reactions

PIQRAY dose level	Dose and schedule	Number and strength of tablets
Starting dose	300 mg/day continuously	2 x 150 mg tablets
First dose reduction	250 mg/day continuously[1]	1 x 200 mg tablet and 1 x 50 mg tablet
Second dose reduction	200 mg/day continuously[2]	1 x 200 mg tablet

[1] Only one dose reduction is permitted for pancreatitis

[2] If further dose reduction below 200 mg/day is required, discontinue PIQRAY

Tables 4-2, 4-3, 4-4 and 4-5 summarize recommendations for dosing interruption, reduction or discontinuation of PIQRAY in the management of specific ADRs. Clinical judgment of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with

PIQRAY.

Hyperglycemia

PIQRAY can cause hyperglycemia. Consultation with a health professional experienced in the treatment of hyperglycemia should always be considered and is recommended for patients with fasting glucose > 250 mg/dL. Patients should be instructed on lifestyle changes that may reduce hyperglycemia.

Dose adjustment should be based on fasting glucose values (Table 4-2). In patients with risk factors for hyperglycemia, monitor fasting glucose more closely and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS).

Table 4-2 Dose modification and management for hyperglycemia

Fasting Glucose (FG)[1]	**Recommendation**
Dose modifications and management should only be based on fasting glucose values (FG; either plasma or blood)	
Grade 1 > ULN - 160 mg/dL or > ULN - 8.9 mmol/L	No PIQRAY dose adjustment required. Initiate or intensify oral anti-diabetic treatment[2].
Grade 2 > 160 - 250 mg/dL or > 8.9 - 13.9 mmol/L	No PIQRAY dose adjustment required. Initiate or intensify oral anti-diabetic treatment[2]. If FG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days with appropriate oral anti-diabetic treatment[2,3], reduce PIQRAY dose by 1 dose level, and follow FG value specific recommendations.
Grade 3 > 250 - 500 mg/dL or > 13.9 - 27.8 mmol/L	Interrupt PIQRAY. Initiate or intensify oral anti-diabetic treatment[2] and consider additional anti-diabetic medications[3] for 1-2 days until hyperglycemia improves, as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). • If FG decreases to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, resume PIQRAY at next lower dose level. • If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, consultation with a physician 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 anti-diabetic treatment[2,3], permanently discontinue PIQRAY treatment.

Fasting Glucose (FG)[1]	Recommendation
Dose modifications and management should only be based on fasting glucose values (FG; either plasma or blood)	
Grade 4 > 500 mg/dL or >27.8 mmol/L	Interrupt PIQRAY. Initiate or intensify appropriate anti-diabetic treatment[2,3] (administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances)). Re-check FG within 24 hours and as clinically indicated. • If FG decreases to ≤ 500 mg/dL or ≤ 27.8 mmol/L, then follow FG value-specific recommendations for < 500 mg/dL. • If FG is confirmed at > 500 mg/dL or > 27.8 mmol/L, permanently discontinue PIQRAY treatment.

[1] Fasting glucose levels reflect hyperglycemia grading according to CTCAE Version 4.03.

CTCAE=Common Terminology Criteria for Adverse Events.

[2] Initiate applicable anti-diabetic medications, such as metformin, SGLT2 inhibitor, or insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors) and review respective prescribing information for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the phase III clinical study with the following guidance: *Initiate metformin 500 mg once daily. Based on tolerability, metformin dose may be increased to 500 mg bid, followed by 500 mg with breakfast, and 1000 mg with dinner, followed by further increase to 1000 mg bid if needed* (see 7 WARNINGS AND PRECAUTIONS).

[3] As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycemia resolves. However, this may not be necessary in the majority of alpelisib-induced hyperglycemia, given the short half-life of alpelisib and the expectation of glucose levels normalizing after interruption of PIQRAY.

Rash and severe cutaneous adverse reactions

PIQRAY can cause rash and severe cutaneous reactions (see 7 WARNINGS AND PRECAUTIONS, Skin). Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with PIQRAY. Based on the severity of rash, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 4-3. Dermatologist consultation is recommended for any severe cutaneous adverse reaction (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme (EM). If a SCAR is confirmed, permanently discontinue PIQRAY.

Table 4-3 Dose modification and management for rash and severe cutaneous adverse reactions

Grade[1,2]	Recommendation
Grade 1 (< 10% body surface area (BSA) with active skin toxicity)	No PIQRAY dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment to manage symptoms. If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid. If the etiology is SCAR, permanently discontinue PIQRAY.
Grade 2	No PIQRAY dose adjustment required.

Grade[1,2]	Recommendation
(10% - 30% BSA with active skin toxicity)	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. If the etiology is SCAR, permanently discontinue PIQRAY.
Grade 3 (e.g., severe rash not responsive to medical management) (> 30% BSA with active skin toxicity)	Interrupt PIQRAY until rash improves to Grade ≤ 1. Initiate or intensify topical/systemic corticosteroid and anti-histamine treatment. If the etiology is SCAR, permanently discontinue PIQRAY. If the etiology is not a SCAR, interrupt dose until improvement to Grade ≤ 1, then resume PIQRAY at next lower dose level.
Grade 4 (e.g.: severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue PIQRAY.
[1] Grading according to CTCAE Version 5.0 [2] For all grades of rash, consider consultation with a dermatologist	

Table 4-4 Dose modification and management for diarrhea or colitis[1]

Grade[1,]	Recommendation
Grade 1	No PIQRAY dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Interrupt PIQRAY dose until improvement to Grade ≤1, then resume PIQRAY at the 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[2].
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.[2,3]

Grade[1,]	Recommendation
Grade 4	Permanently discontinue PIQRAY[3].

[1] Grading according to CTCAE Version 5.0

[2] For Grade 2 and 3 colitis consider additional treatment, such as steroids.

[3] For Grade 3 and 4 diarrhea patients should additionally be managed according to local standard of care, including electrolyte monitoring, administration of anti-emetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.

Other toxicities

Table 4-5 Dose modification and management for other toxicities*

Grade[1]	Recommendation
Grade 1 or 2	No PIQRAY dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt PIQRAY dose until improvement to Grade ≤1, then resume PIQRAY at the next lower dose level[2].
Grade 4	Permanently discontinue PIQRAY.

* Excluding hyperglycemia, rash and severe cutaneous reactions and diarrhea or colitis

[1] Grading according to CTCAE Version 5.0

[2] For Grade 2 and 3 pancreatitis, interrupt PIQRAY dose until improvement to Grade ≤ 1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity re-occurs, permanently discontinue PIQRAY treatment.

[3] For Grade 2 total bilirubin elevation, interrupt PIQRAY dose until improvement to Grade ≤ 1 and resume at the same dose if improved in ≤ 14 days or resume at the next lower dose level if improved in > 14 days.

Refer to the full prescribing information for fulvestrant for dose modification guidelines in the event of toxicity and other relevant safety information.

Special populations

Pediatrics (< 18 years)

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).,

Renal impairment

No dose adjustment is recommended for patients with mild (eGFR 60 to < 90 mL/min/1.73 m^2) and moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2).

The effect of severe renal impairment (eGFR < 30 mL/min/1.73 m^2) on alpelisib pharmacokinetics is unknown (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child-Pugh class A, B or C, respectively) (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Refer to the full prescribing information in the fulvestrant Product Monograph for dose modifications related to hepatic impairment.

4.4. Administration

PIQRAY tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

4.5. Missed Dose

If a dose of PIQRAY is missed, it can be taken immediately following food and within 9 hours after the time it is usually 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. The dose should not be doubled in case of a missed dose.

5. Overdose

There is limited experience of overdose with PIQRAY in clinical studies. In clinical studies, PIQRAY was administered at doses up to 450 mg once daily. Higher incidences of commonly reported adverse events associated with these higher doses were observed, which included, but were not limited to, hyperglycemia, nausea, diarrhea, vomiting, asthenia and rash.

In all cases of over-dosage with PIQRAY, general symptomatic and supportive measures should be initiated. There is no known antidote for PIQRAY.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet 50 mg, 150 mg, 200 mg alpelisib	Film-coated tablet core: hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate Tablet coating: hypromellose, iron oxide black, iron oxide red, macrogol / polyethylene glycol (PEG), talc, titanium dioxide

Description

50 mg PIQRAY tablet: Light pink, unscored, round and curved with bevelled edges, imprinted with "L7" on one side and "NVR" on the other side.

150 mg PIQRAY tablet: Pale red, unscored, ovaloid and curved with bevelled edges, imprinted with "UL7" on one side and "NVR" on the other side.

200 mg PIQRAY tablet: Light red, unscored, ovaloid and curved with bevelled edges, imprinted with "YL7" on one side and "NVR" on the other side.

PIQRAY is supplied in aluminium PVC/PCTFE blisters and are available in the following pack sizes:

300 mg daily dose: each carton contains 4 blister packs. Each blister pack contains a 7-day supply of 14 tablets (56 tablets, 150 mg alpelisib per tablet).

250 mg daily dose: each carton contains 4 blister packs. Each blister pack contains a 7-day supply of 14 tablets (28 tablets, 200 mg alpelisib per tablet and 28 tablets, 50 mg alpelisib per tablet).

200 mg daily dose: each carton contains 2 blister packs. Each blister pack contains a 14-day supply of 14 tablets (28 tablets, 200 mg of alpelisib per tablet).

7. Warnings and Precautions

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Endocrine and Metabolism

Hyperglycemia

Severe hyperglycemia, including Hyperglycemic Hyperosmolar non-ketotic Syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with PIQRAY. Some cases of ketoacidosis with fatal outcome have been reported in the post marketing setting. Hyperglycemia was reported in 66% of patients treated with PIQRAY and 58% of patients managed hyperglycemia with anti-diabetic treatment in the phase III clinical study. Grade 3 (FPG > 250 – 500 mg/dL) and Grade 4 (FPG > 500 mg/dL) hyperglycemia were reported in 34% and 4% of patients, respectively. Patients considered pre-diabetic (FPG > 100 – 125 mg/dL (5.6 – 6.9 mmol/L) and/or HbA1c 5.7% – 6.4%) or diabetic (FPG ≥ 126 mg/dL (≥ 7.0 mmol/L) and/or HbA1c ≥ 6.5%) at baseline were at a higher risk of developing severe hyperglycemia and associated complications (e.g. ketoacidosis). Patients with type I or uncontrolled type II diabetes mellitus were excluded from the phase III clinical study.

Among the patients who had Grade ≥ 2 (FPG > 160 mg/dL) hyperglycemia in the phase III study, the median time to first occurrence of Grade ≥ 2 hyperglycemia was 15 days (range: 5 to 1458 days). The median duration of Grade 2 or higher hyperglycemia was 10 days. The median time to improvement by at least 1 Grade of the first event was 8 days (95% CI of 8 to 10 days). In all patients with elevated FPG, who continued fulvestrant treatment after discontinuing PIQRAY (n=61), 93% of patients returned to baseline (normal).

Hyperglycemia was manageable with appropriate oral anti-diabetic therapy and PIQRAY dose modifications or discontinuation (see 4 DOSAGE AND ADMINISTRATION, Table 4-2). Among the 191 patients with reported hyperglycemia event, 87% of patients were managed with anti-diabetic medication, (e.g. metformin), 40% of patients with dose interruption, 43% of patients with dose reduction, and 10% of patients with permanent discontinuation. In patients with hyperglycemia, 166/191 (87%) were managed with anti-diabetic medication and 145/191 (76%) reported use of metformin as single agent or in combination with other anti-diabetic medication. The maximum dose of metformin recommended in phase III clinical study was 2,000 mg per day.

In the phase III clinical study, patients with a history of diabetes mellitus intensified anti-diabetic medication(s) while on treatment with PIQRAY; therefore, these patients require monitoring and possibly intensified anti-diabetic treatment. Patients with poor glycemic control may be at a higher risk of developing severe hyperglycemia and associated complications. Patients with risk factors for hyperglycemia such as obesity (BMI ≥30), elevated FPG or HbA1c at or above the upper limit of normal, or age ≥75 are at a higher risk of developing severe hyperglycemia. Schedule for monitoring fasting glucose is presented in Table 7-1 (see Monitoring and Laboratory Tests).

Advise patients of the signs and symptoms of hyperglycemia (e.g. excessive thirst, urinating more often than usual or higher amount of urine than usual, increased appetite with weight loss).

Correct glucose levels in patients with abnormal glucose levels before initiating PIQRAY, and closely monitor glucose levels to enable early detection and early treatment of hyperglycemia.

In the METALLICA study, premedication with metformin, initiated 7 days prior to the start of treatment with PIQRAY, appeared to decrease the incidence and severity of hyperglycemia events, but increase the incidence of diarrhea, nausea, and vomiting, including Grade 3 diarrhea (see 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS). Premedication with metformin prior to PIQRAY plus fulvestrant treatment should be considered based on patient risk factors for hyperglycemia and gastrointestinal tolerability.

Gastrointestinal

Diarrhea or Colitis, nausea and vomiting

Severe diarrhea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with PIQRAY (see 8 ADVERSE REACTIONS). In the phase III clinical study, Grade 2 and 3 diarrhea was reported in 20% and 7% of patients treated with PIQRAY, respectively.

There were no reported cases of Grade 4 diarrhea. Grade 3 gastrointestinal events (mostly diarrhea) were reported in 10% of patients and serious gastrointestinal events in 5% of patients. Among patients with Grade 2 or 3 diarrhea, median time to onset of the first event was 54 days (range: 1 to 1731 days). Anti-emetics (e.g., ondansetron) and anti-diarrheal medications (e.g., loperamide) were used in 19% and 65% of patients to manage gastrointestinal symptoms.

In the phase III clinical study, dose reductions of PIQRAY were required in 6% of patients and 3% of patients permanently discontinued PIQRAY due to diarrhea.

Colitis has been reported in the post marketing setting in patients treated with PIQRAY (see 8 ADVERSE REACTIONS).

Patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Based on the severity of the diarrhoea or colitis, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 4-4 (see 4 DOSAGE AND ADMINISTRATION). Dose modifications of PIQRAY are recommended in patients with Grade ≥ 2 diarrhea.

Patients should be advised to notify their healthcare provider if diarrhea or additional symptoms of colitis occur while taking PIQRAY. Patients experiencing gastrointestinal toxicity should be managed according to local standards of care, including electrolyte monitoring, administration of anti-emetics and antidiarrheal medications and/or fluid replacement and electrolyte supplements, as clinically indicated.

In case of colitis, additional treatment, such as steroids, may be considered as clinically indicated.

Immune

Hypersensitivity and anaphylactic reaction

Serious hypersensitivity reactions including anaphylactic reaction and anaphylactic shock, manifested by symptoms including, but not limited to, dyspnoea, flushing, rash, fever or tachycardia were reported in patients treated with PIQRAY in clinical trials. In the phase III clinical trial, hypersensitivity events were reported in 18% of patients treated with PIQRAY. The most common adverse events reported were

hypersensitivity (4%), face oedema (4%) and swelling face (2%). The incidence of serious hypersensitivity reaction was 2%. Hypersensitivity and anaphylactic reactions were more common in Asian patients compared to other races. Angioedema has been reported in the post marketing setting in patients treated with PIQRAY (see 8 ADVERSE REACTIONS). PIQRAY should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions (see 2 CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Patients should be monitored for Hyperglycemia.

Table 7-1 Schedule of fasting glucose monitoring

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with PIQRAY	**Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with PIQRAY**
At screening, before initiating treatment with PIQRAY	Test for fasting plasma glucose (FPG), HbA1c, and optimize the patient's level of blood glucose.	
After initiating treatment with PIQRAY	Monitor/self-monitor fasting glucose at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated, according to the instructions of a healthcare professional*.	Monitor/self-monitor fasting glucose more frequently for the first few weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycemia according to the instructions of a healthcare professional*.
	HbA1c should be monitored every 3 months as clinically indicated.	
If hyperglycemia develops after initiating treatment with PIQRAY	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.	
	During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycemia.	

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

Musculoskeletal

Osteonecrosis of the jaw (ONJ)

In the phase III clinical study, osteonecrosis of the jaw (ONJ) was reported in 6% of patients in the PIQRAY plus fulvestrant arm, including 3% with a serious event. All patients experiencing ONJ were also exposed to prior or concomitant bisphosphonates or RANK-ligand inhibitors (e.g. denosumab). Caution should be exercised when PIQRAY and drugs known to cause ONJ are used either simultaneously, or sequentially. PIQRAY treatment should not be initiated in patients with ongoing ONJ. Patients should be advised to promptly report any new or worsening oral symptoms (such as dental mobility, pain or swelling, non-healing of mouth sores, or discharge) during treatment with PIQRAY. A dental examination with appropriate preventive dentistry is recommended prior to treatment with PIQRAY in patients with risk factors for ONJ, such as invasive dental procedures, concomitant therapies, poor oral hygiene and comorbid disorders.

In patients who develop ONJ, standard medical management should be initiated, including maintaining good oral hygiene, controlling pain and treating areas of infection with antibiotics and oral antibiotic mouth rinses. Patients should have appropriate nutrition and oral fluid intake.

Reproductive Health

Reproduction

The pregnancy status for females of reproductive potential should be verified prior to starting treatment with PIQRAY.

Females of reproductive potential should be advised of the potential harm to the developing foetus (see 15 NON-CLINICAL TOXICOLOGY). Advise sexually-active females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) when using PIQRAY, during treatment and for at least 1 week after stopping treatment. It is currently unknown whether PIQRAY may reduce the effectiveness of systemically acting hormonal contraceptives.

Advise male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant, to use condoms during sexual intercourse while taking PIQRAY and for at least 1 week after stopping treatment with PIQRAY. Male patients are also advised not to donate or store semen during treatment and at least 1 week after the last dose of PIQRAY.

Fertility

There are no clinical data available on the effect of PIQRAY on human fertility. Based on repeated dose toxicity studies in animals, PIQRAY may impair fertility in males and females of reproductive potential. In fertility studies conducted in male and female rats, similar effects were observed

Respiratory

Pneumonitis

Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, have been reported in clinical trials. In the phase III clinical study, pneumonitis was reported in 5 (2%) of patients treated with PIQRAY (see 8 ADVERSE REACTIONS). Advise patients 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, interrupt PIQRAY treatment immediately and evaluate the patient for pneumonitis. Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, cough, dyspnoea, 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.

Skin

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions have been reported with PIQRAY (see 8 ADVERSE REACTIONS). In the phase III study, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 1 (< 1%) and 3 (1%) patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post marketing setting. Do not initiate PIQRAY treatment in patients with history of severe cutaneous reactions.

Advise patients of the signs and symptoms of severe cutaneous adverse reactions (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of severe cutaneous adverse reactions are present, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a severe cutaneous adverse reaction is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous severe cutaneous adverse reactions. If a severe cutaneous adverse reaction is not confirmed, PIQRAY treatment may require interruption, dose reduction, or discontinuation as described in Table 4-3 Dose modification and management for rash and severe cutaneous adverse reactions (see 4 DOSAGE AND ADMINISTRATION).

Rash

In the phase III clinical study, rash (including rash maculo-papular, rash macular, rash generalised, rash papular, rash pruritic, dermatitis and dermatitis acneiform) were reported in 54% patients treated with PIQRAY plus fulvestrant. Rash as serious adverse events and discontinuation of PIQRAY due to a rash was reported in 3.5% and 4.2% of patients, respectively. Grade ≥ 2 rash were reported in 34% and the median time to first onset was 12 days (range: 2 to 220 days). Antihistamines, topical or systemic low-dose corticosteroids, and PIQRAY dose modification (see 4 DOSAGE AND ADMINISTRATION) were used to manage rash.

7.1. Special Populations

7.1.1 Pregnancy

There are no data regarding the use of PIQRAY in pregnant women. Embryo-foetal development studies have demonstrated that oral administration of alpelisib during organogenesis increased embryo-foetal death and teratogenicity in rats and rabbits, at doses below the exposure in humans (see 15 NON-CLINICAL TOXICOLOGY). Based on the animal data and its mechanism of action, PIQRAY can cause foetal harm when administered to a pregnant woman.

Do not use PIQRAY during pregnancy and in women of childbearing potential not using effective contraception. If the patient becomes pregnant while taking PIQRAY, inform the patient of the potential hazard to the foetus.

7.1.2 Breastfeeding

It is not known if alpelisib is transferred into human or animal milk after administration of PIQRAY. There are no data on the effects of alpelisib on the breastfed child or the effects of alpelisib on milk production.

Because of the potential for serious adverse reactions in the breastfed child from PIQRAY, it is recommended that women should not breastfeed during treatment and for at least 1 week after the last dose of PIQRAY.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for paediatric use.

7.1.4 Geriatrics

Of the 284 patients who received PIQRAY plus fulvestrant in the phase III study, 41% of the patients were ≥ 65 years of age, including 12% ≥ 75 years of age. No overall differences in safety or effectiveness of PIQRAY were observed between these patients and younger patients; however, gastrointestinal toxicity (primarily diarrhea and nausea), hyperglycemia, weight decreased, hypokalaemia and dyspnoea were reported more frequently in older patients.

7.1.5 Race

Of the 284 patients who received PIQRAY plus fulvestrant in the phase III study, 21% of the patients were Asians. Rash, severe cutaneous reactions, hypersensitivity and anaphylactic reaction, and pancreatitis were more frequently reported in Asian patients compared to Caucasian patients.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The overall safety evaluation of PIQRAY is based on data from the phase III clinical study of 572 patients (571 post-menopausal women and 1 male patient) who were enrolled into two cohorts, with or without a PIK3CA mutation. Patients were then randomized in a 1:1 ratio to receive PIQRAY plus fulvestrant or placebo plus fulvestrant. Overall, in the safety set (n=571), 284 patients received PIQRAY in combination with fulvestrant at the recommended starting dose of 300 mg, and 287 patients received placebo in combination with fulvestrant.

The median duration of exposure to PIQRAY plus fulvestrant was 8.2 compared to 5.6 months to placebo and fulvestrant.

Almost all patients (99%) in the PIQRAY plus fulvestrant group (vs. 93% in the placebo plus fulvestrant group) experienced at least one adverse event (AEs). The most common adverse reactions (ADRs) in PIQRAY plus fulvestrant-treated patients (reported at a frequency ≥ 20% and for which the frequency for PIQRAY plus fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycemia, diarrhea, rash, nausea, fatigue and asthenia, decreased appetite, stomatitis, vomiting, weight decreased and alopecia.

Severe (Grade 3 or 4) AEs were more frequently reported in the PIQRAY plus fulvestrant group (79% vs. 37% in the placebo plus fulvestrant arm). The most common Grade ≥ 3 adverse reactions (reported at a frequency ≥ 2% in the PIQRAY plus fulvestrant arm and for which the frequency for PIQRAY plus

fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycemia, rash and maculo-papular rash, diarrhea, lipase increased, hypertension, hypokalaemia, weight decreased, fatigue and asthenia, anaemia, nausea, osteonecrosis of jaw, stomatitis, alanine aminotransferase increased, lymphopenia, mucosal inflammation and acute kidney injury.

Two patients died during treatment with PIQRAY plus fulvestrant due to causes other than the underlying disease (one cardio-respiratory arrest and one second primary malignancy). Neither was considered related to treatment with PIQRAY.

PIQRAY dose reductions due to AEs, regardless of causality, occurred in 60% of patients receiving PIQRAY plus fulvestrant and in 5% of patients receiving placebo plus fulvestrant. Permanent discontinuation of PIQRAY and/or fulvestrant due to AEs were reported in 26% of patients receiving PIQRAY plus fulvestrant, compared to 6% of patients receiving placebo plus fulvestrant. The most common AEs leading to treatment discontinuation of both PIQRAY and fulvestrant were hyperglycemia (6%), rash (3%), diarrhea (3%) and fatigue (2%).

8.2. Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions from the phase III clinical study (Table 8-1) are listed by MedDRA system organ class and ranked by frequency within each system organ class.

Table 8-1 Adverse reactions occurring in ≥ 10% of patients and with ≥ 2% higher incidence in the PIQRAY arm (all grades) in the phase III SOLAR-1 study

	PIQRAY plus fulvestrant N = 284			Placebo plus fulvestrant N = 287		
System organ class/preferred term	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Blood and lymphatic system disorders						
Anaemia	13	5	0	7	1	0
Hypertension	11	5	<1	6	4	0
Gastrointestinal disorders						
Diarrhea	60	7	0	17	<1	0
Nausea	47	3	0	23	<1	0
Stomatitis[1]	31	3	0	7	0	0
Vomiting	30	<1	0	10	<1	0
Abdominal pain	19	1	0	12	1	0

	PIQRAY plus fulvestrant N = 284			Placebo plus fulvestrant N = 287		
Dyspepsia	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue[2]	44	6	0	30	1	0
Mucosal inflammation	20	2	0	1	0	0
Oedema peripheral	17	0	0	6	<1	0
Pyrexia	17	<1	<1	6	<1	0
Mucosal dryness[3]	13	<1	0	5	0	0
Infections and infestations						
Urinary tract infection[4]	10	<1	0	6	1	0
Investigations						
Weight decreased	28	6	0	2	0	0
Blood creatinine increased	13	2	0	1	0	0
Metabolism and nutrition disorders						
Hyperglycemia	66	34	4	10	<1	<1
Decreased appetite	37	1	0	11	<1	0
Hypokalaemia	11	4	1	2	<1	0
Nervous system disorders						
Dysgeusia[5]	16	<1	0	3	0	0
Headache	19	<1	0	13	0	0
Skin and subcutaneous tissue disorders						
Rash[6]	52	19	0	8	<1	0
Alopecia	20	0	0	2	0	0
Pruritus	19	<1	0	7	0	0
Dry skin[7]	19	<1	0	4	0	0

Grading according to CTCAE Version 4.03

[1] Stomatitis: including stomatitis, aphthous ulcer and mouth ulceration

[2] Fatigue: including fatigue, asthenia

[3] Mucosal dryness: including dry mouth, mucosal dryness, vulvovaginal dryness

[4] Urinary tract infection: including UTI and single case of urosepsis

[5] Dysgeusia : including dysgeusia, ageusia, hypogeusia

[6] Rash: including rash, rash maculo-papular, rash macular, rash generalized, rash papular, rash pruritic

[7] Dry skin: including dry skin, skin fissures, xerosis, xeroderma

METALLICA (Prophylaxis Management of Hyperglycemia)

The METALLICA study was a multicenter, open-label, single-arm, two-cohort study evaluating the safety of premedication with metformin prior to treatment with PIQRAY in combination with endocrine therapy in patients with HR-positive, HER2-negative advanced breast cancer harboring PIK3CA mutation(s).

A total of 68 patients were enrolled in one of two cohorts. Cohort A enrolled 48 patients with normal glycemic status (FPG <100 mg/dL [<5.6 mmol/L] and HbA1c <5.7%) and cohort B enrolled 20 patients with impaired glycemic status (FPG 100 to 140 mg/dL [5.6 to 7.8 mmol/L] or HbA1c 5.7 to 6.4%). The majority of patients (63/68, 93% [45 in cohort A, 18 in cohort B]) received fulvestrant as endocrine therapy during the study.

Metformin was initiated 7 days prior to the start of treatment with PIQRAY, administered at a dose of 500 mg twice daily from day 1 to day 3, thereafter increased up to 1,000 mg twice daily based on tolerability.

The primary objective was to assess the occurrence of Grade 3/4 hyperglycemic events in the first two cycles of treatment. Grade 3/4 hyperglycemia occurred in 2% of patients in cohort A and 15% of patients in cohort B, with the overall incidence of any Grade hyperglycemia adverse events being 33% (16/48 patients) and 70% (14/20 patients) in cohorts A and B, respectively. The incidence of nausea, vomiting, and diarrhea adverse reactions, including Grade 3 diarrhea, increased with metformin premedication (see 7 WARNINGS AND PRECAUTIONS).

The most common AEs (≥30%) in the study overall were diarrhea (68%), nausea (68%), fatigue (46%), hyperglycemia (44%), rash (38%) and vomiting (34%). The most common Grade 3/4 AEs (≥5%) were rash (16%), diarrhea (13%) and hyperglycemia (6%). Serious adverse reactions occurred in 22% of patients overall, and included (≥2%) diarrhea (3%), rash (3%), and vomiting (3%).

Dose adjustment or interruption of PIQRAY due to adverse events occurred in 56% of patients, of which 28% were dose reductions. Permanent discontinuation of PIQRAY due to adverse reactions occurred in 19% of patients.

8.3. Less Common Clinical Trial Adverse Reactions

Other clinically significant adverse drug reactions reported in < 10% of patients and with higher incidences reported in the PIQRAY arm (all grades) are presented below.

Blood and lymphatic system disorders: lymphopenia (6%), thrombocytopenia (3%)

Eye disorders: vision blurred (5%), dry eye (4%)

Gastrointestinal disorders: toothache (5%), gingivitis (4%), cheilitis (3%), gingival pain (4%), pancreatitis (<1%)

General disorders and administration site conditions: oedema (7%)

Immune system disorders: hypersensitivity (4%)

Investigations: gamma-glutamyltransferase increased (9.9%), alanine aminotransferase increased (9.9%), lipase increased (8%), glycosylated haemoglobin increased (3%)

Metabolism and nutrition disorders: hypocalcaemia (4%), dehydration (4%), ketoacidosis[1] (1%)

Musculoskeletal and connective tissue disorders: muscle spasms (8%), myalgia (7%), osteonecrosis of jaw (6%)

Psychiatric disorders: insomnia (8%)

Renal and urinary disorders: acute kidney injury (6%)

Respiratory, thoracic and mediastinal disorders: pneumonitis[2] (2%)

Skin and subcutaneous tissue disorders: erythema[3] (7%), dermatitis[4] (4%), palmar-plantar erythrodysaesthesia syndrome (2%), erythema multiforme (1%), Stevens-Johnson syndrome (<1%)

Vascular disorders: lymphedema (6%)

[1] Including diabetic ketoacidosis
[2] Including interstitial lung disease
[3] Including erythema generalized
[4] Including dermatitis acneiform

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Table 8-2 Laboratory abnormalities occurring in ≥ 10% of patients and with ≥ 5% incidence in the PIQRAY plus fulvestrant arm in the phase III SOLAR-1 study

	PIQRAY plus fulvestrant N = 284			Placebo plus fulvestrant N = 287		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Haematological parameters						
Lymphocyte decreased	56	9	1	41	5	0
Haemoglobin decreased	45	5	0	30	2	0
Activated Partial Thromboplastin Time increased	24	<1	0	19	<1	0
Platelet decreased	15	<1	<1	7	<1	0
Biochemical parameters						
Glucose increased	79	34	6	35	1	<1
Creatinine increased	68	3	<1	27	<1	0
Gamma Glutamyl Transferase increased	54	11	1	46	9	2
Alanine Aminotransferase increased	45	4	1	35	2	0
Lipase, Pancreatic increased	43	6	1	27	5	1

	PIQRAY plus fulvestrant N = 284			Placebo plus fulvestrant N = 287		
Calcium Corrected decreased	28	2	<1	20	<1	1
Glucose decreased	28	0	<1	14	0	0
Potassium decreased	15	5	1	3	<1	0
Albumin decreased	16	<1	0	8	0	0
Magnesium decreased	13	<1	0	5	0	0

8.5. Post-Market Adverse Reactions

Eye disorders: Uveitis.

Gastrointestinal disorders: Colitis.

Metabolism and nutrition disorders: Hyperglycemic Hyperosmolar nonketotic Syndrome (HHNKS).

Skin and subcutaneous tissue disorders: Angioedema, Drug reaction with eosinophilia and systemic symptoms (DRESS).

9. Drug Interactions

9.2. Drug Interactions Overview

In-vitro assessment of drug interactions

Alpelisib inhibits CYP3A4 in a time-dependent manner and induces cytochromes CYP2B6, CYP2C9 and CYP3A4.

Alpelisib is an inhibitor of P-gp (P-glycoprotein). Alpelisib has a low potential to inhibit BCRP (Breast Cancer Resistance Protein), MRP2 (Multidrug Resistance-associated Protein 2), BSEP (Bile Salt Export Pump), OATP1B1 (Organic Anion Transporting Polypeptide 1B1), OATP1B3 (Organic Anion Transporting Polypeptide 1B3), OCT1 (Organic Cation Transporter 1), OAT1 (Organic Anion Transporter 1), OAT3 (Organic Anion Transporter 3), OCT2 (Organic Cation Transporter 2), MATE1 (Multidrug And Toxin Extrusion Protein 1), and MATE2K (Multidrug and Toxin Extrusion Protein 2-K) at clinically relevant concentrations.

Alpelisib is a substrate for BCRP transporter.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 9-1 Established or potential drug-drug interactions

[Proper/ Common name]	Source of Evidence	Effect	Clinical comment

Effect of PIQRAY on other drugs			
CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2B6substrates	CT	In a drug-drug interaction study, co-administration of repeated doses of alpelisib 300 mg with a single-dose of sensitive substrates of CYP3A4 (midazolam), CYP2C8 (repaglinide), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP2B6 (bupropion), administered as a cocktail, showed that there is no clinically significant pharmacokinetic interaction. Co-administration with PIQRAY increased exposure (AUC) for omeprazole (+7%), bupropion (+15%), and repaglinide (37%), Co-administration with PIQRAY had no change for midazolam exposure (-1%). The magnitude of interaction observed is not considered clinically relevant. Exposure (AUC) of S-warfarin and R-warfarin increased (34% and 21%, respectively) when co-administered with PIQRAY but no effect was observed on prothrombin time, hence the magnitude of interaction is not clinically relevant.	No dose adjustment is required when administering PIQRAY with CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2B6 substrates.
CYP3A4 and P-gp substrates	CT	No clinically significant differences in pharmacokinetics of everolimus (a substrate of CYP3A4 and P-gp) were observed when co-administered with alpelisib in patients with advanced solid tumours. The C_{max} of everolimus increased by 11% and the AUC0-24 decreased by 11% on co-administration with alpelisib and is not considered clinically meaningful.	No dose adjustment is required when administering PIQRAY with a CYP3A4 substrate (e.g., everolimus). A clinically relevant effect of PIQRAY on P-gp substrates can be excluded.

Effect of other drugs on PIQRAY			
CYP3A4 inducers	CT	Co-administration of PIQRAY with a strong CYP3A4 inducer decreases alpelisib area under the curve (AUC) (see 10, CLINICAL PHARMACOLOGY), which may reduce alpelisib efficacy. Administration of 600 mg once daily rifampin, a strong CYP3A4 inducer, for 7 days, before co-administration with a single oral 300 mg PIQRAY dose on Day 8, decreased alpelisib Cmax by 38% and AUC by 57% in healthy adults (N = 25). Administration of 600 mg once daily rifampin for 15 days, coadministered with daily 300 mg alpelisib starting from Day 8 to Day 15 decreased the steady state alpelisib Cmax by 59% and AUC by 74%.	Co-administration of alpelisib with strong CYP3A4 inducers (e.g., apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) should be avoided and selection of an alternative concomitant medicinal product, with no or minimal potential to induce CYP3A4, should be considered (see 10, CLINICAL PHARMACOLOGY)
BCRP inhibitors	in vitro data	Co-administration of PIQRAY with a BCRP inhibitor (e.g., cyclosporine, eltrombopag, lapatinib) may increase alpelisib concentration, which may increase the risk of toxicities.	Caution with the use of BCRP inhibitors in patients treated with PIQRAY. If unable to use alternative drugs, closely monitor for increased adverse reactions when PIQRAY is used in combination with BCRP inhibitors.
Acid-reducing agents	CT	Co-administration of the H2 receptor-antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib decreased the absorption and overall exposure of alpelisib. In the presence of a low-fat low-calorie meal, AUC was decreased on average by 21% and Cmax by 36% with ranitidine. Under the fasted state, AUC was decreased on average by 30% and Cmax by 51% when co-administered with ranitidine based on the results of the clinical study.	PIQRAY can be co-administered with acid reducing agents, since PIQRAY should be taken with food. Food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value.

Fulvestrant	CT	Clinical study data in patients with breast cancer indicated no effect of fulvestrant on alpelisib exposure (and vice versa) following co-administration of these drugs.	N/A
Drugs known to cause QTc prolongation	CT	PIQRAY treatment is associated with QT prolongation. An analysis of clinical ECG data showed mean increases from baseline in QTcF were 8.7 ms (90% CI: 4.1, 13.3) in patients treated with PIQRAY at the clinically recommended dose (see 10 CLINICAL PHARMACOLOGY, Pharmacodynamics).	Caution should be taken if PIQRAY is used concomitantly with medicinal products that are known to prolong the QTc interval, and perform additional ECG monitoring as clinically indicated.

Legend: CT = Clinical Trial

9.5 Drug-Food Interactions

In healthy patients, co-administration of alpelisib with food resulted in an increased AUC of alpelisib by 77% (see 10 CLINICAL PHARMACOLOGY and 4. DOSAGE AND ADMINISTRATION).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Alpelisib is an inhibitor of phosphatidylinositol3kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PI3Kα encoded by the PIK3CA gene) lead to activation of PI3Kα and Akt-signalling, cellular transformation and the generation of tumours in *in vitro* and *in vivo* models. In biochemical assays, alpelisib inhibited wild type PIK3α (IC_{50} = 4.6 nmol/L) and its two most common somatic mutations (H1047R, E545K) (IC_{50} ~ 4 nmol/L) more potently than the PI3Kδ (IC_{50} = 290 nmol/L) and PI3Kγ (IC_{50} = 250 nmol/L) isoforms and showed significantly reduced activity against PI3Kβ (IC_{50} = 1156 nmol/L).

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt, and showed activity in cell lines harbouring a PIK3CA mutation. *In vivo*, alpelisib inhibited the PI3K/Akt signalling pathway and reduced tumour growth in xenograft models, including models of breast cancer. PI3K inhibition by alpelisib treatment has been shown to induce an increase in oestrogen

receptor (ER) transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased anti-tumour activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA-mutated breast cancer cell lines.

10.2. Pharmacodynamics

Hyperglycemia

Hyperglycemia is an on-target effect of PI3K signalling pathway inhibition and alpelisib treatment has the potential to interfere with glucose and insulin homeostasis. Alpelisib, at concentrations > 20 µmol/L, produced a concentration-dependent glucose increase which led to hyperglycemia despite elevation of insulin plasma levels. In non-clinical studies with alpelisib, pancreas was identified as a secondary target organ due to changes in peripheral glucose uptake.

QT_C prolongation

In vitro, the IC_{50} of alpelisib for the inhibition of hERG transmission was 9.4 µM, using voltage-clamped human embryonic kidney cells (HEK293), which is similar to mean C_{max} (6.8 µM) and ~13-fold higher than the unbound C_{max} (0.71 µM) in patients at the clinically recommended dose (300 mg). No relevant electrophysiological effect was seen in dogs.

A dedicated QTc study has not been conducted. ECGs were collected in a phase I study to evaluate the effect of alpelisib on the QTcF interval. In patients administered a 300 mg dose (n = 14), the mean QTcF change from baseline was 8.7 msec (90% CI: 4.1, 13.3) at the observed C_{max} at steady-state.

10.3. Pharmacokinetics

The pharmacokinetics of alpelisib has been studied in healthy volunteers and adult patients with solid tumours. Steady-state alpelisib maximum plasma concentration (C_{max}) and AUC increased proportionally over the dose range of 30 mg to 450 mg (0.1 to 1.5 times the approved recommended dosage of 300 mg QD) under fed conditions. The mean accumulation of alpelisib is 1.3 to 1.5 fold and steady-state plasma concentrations are reached within 3 days following daily dosage. In adult patients who received PIQRAY 300 mg once daily in the SOLAR-1 trial, mean steady-state alpelisib C_{max} was 2480 ng/mL and AUC_{tau} was 33224 ng*h/mL based on a population approach analysis. The geometric mean AUC_{inf} was reduced by 37% and the C_{max} was comparable in healthy volunteers compared to cancer patients administered alpelisib 300 mg single dose. Alpelisib exhibits low clearance with 9.4 L/hr based on population PK analysis under fed conditions. The population-derived half-life, independent of dose and time, was around 9 hours at steady state of 300 mg, once daily.

Table 10.1 Summary of alpelisib pharmacokinetic parameters[1] in patients with solid tumours (including breast cancer) under fed conditions

Dose	C_{max} (ng/mL) (CV%)	T_{max} (h) (CV%)	$t_{½}$ (h) (CV%)	AUC_{tau} (ng*h/mL) (CV%)	CL (L/h) (CV)	Vd (L) (SV%)
300 mg, multiple dose	2480 (23)	4.6 (4)	9 (3.7)	33224 (21)	9.4 (19)	121 (35)

Dose	C_{max} (ng/mL) (CV%)	T_{max} (h) (CV%)	$t_{½}$ (h) (CV%)	AUC_{tau} (ng*h/mL) (CV%)	CL (L/h) (CV)	Vd (L) (SV%)

[1] Phase III population PK model estimates and derived PK parameters at 300 mg once daily

Values denote arithmetic mean and median for T_{max}.

Absorption: Following oral administration of alpelisib, median time to reach peak plasma concentration (T_{max}) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen.

Food effect: Alpelisib absorption is affected by food. Co-administration of a single 300 mg oral dose of alpelisib, with a high-fat high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased AUC by 73% and C_{max} by 84%, and co-administration with a low-fat low-calorie (LFLC) meal (334 calories with 8.7 g of fat) increased AUC by 77% and C_{max} by 145%. No significant difference in alpelisib AUC was observed between LFLC and HFLC meals (see 4 DOSAGE AND ADMINISTRATION).

Distribution: The mean apparent volume of distribution of alpelisib at steady-state (V_{ss}/F) is predicted to be 114 L. Protein binding of alpelisib is 89% and is independent of concentration.

Metabolism: Alpelisib is primarily metabolised by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4-mediated hydroxylation, *in vitro*. BZG791 accounted for approximately 40-45 % of the dose, CYP3A4-mediated metabolites and glucuronides amounted to approximately 15% of the dose. The rest of the dose, which was found as unchanged alpelisib in urine and feces, was either excreted as alpelisib or non-absorbed.

Elimination: Following a single oral dose of 400 mg radiolabelled alpelisib under fasted condition, 81% of the administered dose were primarily found in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine. The elimination of alpelisib is majorly driven by non-hepatic hydrolysis mediated by multiple enzymes (esterases, amidases, choline esterase) and, to a lesser degree, CYP3A4 mediated metabolism (hydroxylation). The contribution of hepatobiliary export or intestinal secretion via BCRP in human is considered to be low.

Special Populations and Conditions

Paediatrics (below 18 years): The pharmacokinetics of PIQRAY in paediatric patients have not been established.

Geriatrics (65 years or above): Age had no clinically relevant effect on the pharmacokinetics of alpelisib based on population pharmacokinetic analysis. The CL of alpelisib decreased by 5% for patients 10 years older than average, with a median age of 62 years (range 25 to 87 years) based on population pharmacokinetic analysis of the phase III clinical data (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Gender

Gender had no clinically relevant effect on the pharmacokinetics of alpelisib based on the population pharmacokinetic analysis. The $AUC_{0\text{-}24,\,ss}$ in males were lower by 25% compared to females, based on population pharmacokinetic analysis.

Body Weight

Body weight had no clinically relevant effect on the pharmacokinetics of alpelisib based on the population pharmacokinetic analysis. Compared to the typical patient weighing 67 kg, for a patient weighing 50 or 90 kg, $AUC_{0\text{-}24,\,ss}$ was estimated to be higher by 20% or lower by 17%, respectively.

Race/Ethnicity: Race had no clinically relevant effect on the pharmacokinetics of alpelisib based on the population pharmacokinetic analysis and a single agent study in Japanese cancer patients. The C_{max} were higher by 19% in Japanese patients compared to non-Japanese patients, while the AUC's were comparable based on a population pharmacokinetic analysis (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Race).

Hepatic Impairment: In patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) administered a single dose of alpelisib 300 mg QD, the total AUC_{inf} and C_{max} of alpelisib decreased by approximately 27% and 17% and the unbound AUC_{inf} and C_{max} decreased by 20% and 15% in patients with moderate hepatic impairment compared to patients with normal hepatic function. The total AUC_{inf} and C_{max} of alpelisib increased by approximately by 25% and 0%, and the unbound AUC_{inf} and C_{max} increased by 73% and 36% in patients with severe hepatic impairment compared to patients with normal hepatic function, based on the results of a hepatic impairment study in non-cancer patients. Mild hepatic impairment (Child-Pugh A) had no clinically relevant effect on the pharmacokinetics of alpelisib based on the population pharmacokinetic analysis (see 4 DOSAGE AND ADMINISTRATION).

Renal Impairment: Based on a population pharmacokinetic analysis that included 117 patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2)/(CL_{cr} ≥ 90 mL/min), 108 patients with mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m^2)/(CL_{cr} 60 to < 90 mL/min), and 45 patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2), the $AUC_{0\text{-}24,\,ss}$ of alpelisib increased by 2% and 8% in patients with mild and moderate renal impairment compared to patients with normal renal function. These increases in exposures are not considered clinically relevant. The effect of severe renal impairment (eGFR < 30 mL/min/1.73 m^2) on alpelisib pharmacokinetics is unknown (see 4 DOSAGE AND ADMINISTRATION).

Genetic Polymorphism: The effects of genetic polymorphism on the pharmacokinetics of alpelisib have not been evaluated.

11. Storage, Stability, and Disposal

Do not store above 30°C. Store in the original package to protect from moisture.

PIQRAY must be kept out of the reach and sight of children.

Part 2: Scientific Information

13. Pharmaceutical Information

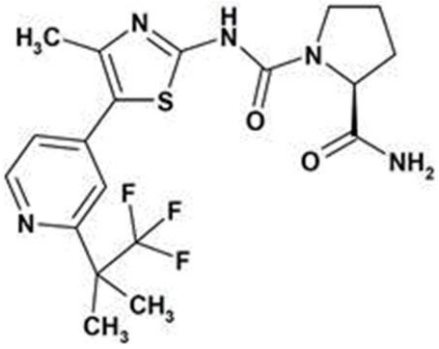
Drug Substance

Non-proprietary name of the drug substance: Alpelisib

Chemical name: (2S)-1-N-{4-Methyl-5- [2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl} pyrrolidine-1,2-dicarboxamide

Molecular formula and molecular mass: $C_{19}H_{22}F_3N_5O_2S$
441.47

Structural formula:



Physicochemical properties: White to practically white powder
pH dependent solubility: soluble in low (acidic) pHs and insoluble in high (alkaline) pHs

Solvent	Solubility (mg/mL)
Water	0.02
pH 1.0 (HCl 0.1 N)	3.64
pH 2.0 (HCl 0.01 N)	0.42
Buffer pH 4.0 (acetate)	0.03
Buffer pH 5.0 (acetate)	0.02
Buffer pH 6.8 (phosphate)	0.02

14. Clinical Trials

14.1. Clinical Trials by Indication

PIQRAY (alpelisib), is indicated in combination with fulvestrant, for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative, PIK3CA- mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen.

PIQRAY was evaluated in a pivotal phase III, randomized, double-blind, placebo-controlled study (SOLAR-1) of PIQRAY in combination with fulvestrant in men and postmenopausal women with hormone

receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer whose disease had progressed or recurred on or after an endocrine-based treatment. Patients with inflammatory breast cancer, symptomatic visceral disease, prior treatment of chemotherapy, or concurrently using other anticancer therapy, active CNS metastases, diabetes mellitus type I or uncontrolled type II, or clinically significant, uncontrolled heart disease and/or recent cardiac events (including long QT syndrome, QTcF > 450 ms for males or > 460 ms for females) at baseline were excluded.

Based on PIK3CA mutation tests using tumour tissue, a total of 572 HR-positive, HER2-negative patients were enrolled into two cohorts: PIK3CA mutation cohort or PIK3CA non-mutation cohort. PIK3CA mutation status in Exons 7, 9 and 20 (Exon 7: C420R; Exon 9: E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and Exon 20: H1047L, H1047R, H1047Y) was determined by a validated real-time PCR sequencing assay. Overall, 60% of enrolled patients (n = 341) had tumours with one or more PIK3CA mutations and 40% (n = 231) had tumours without a PIK3CA mutation.

In each cohort, patients were randomized to receive either PIQRAY 300 mg plus fulvestrant or placebo plus fulvestrant in a 1:1 ratio. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s).

PIQRAY 300 mg or matching placebo was administered orally once daily on a continuous basis. Fulvestrant 500 mg was administered intramuscularly on Cycle 1 Day 1 and 15 and then at Day 1 of a 28-day cycle (administration +/- 3 days). Patients were not allowed to cross over from placebo to PIQRAY during the study or after disease progression. Patients were treated until disease progression or unacceptable toxicity. Overall, the median treatment duration was 8.2 months in the PIQRAY plus fulvestrant arm and 5.6 months in the placebo plus fulvestrant arm.

The primary endpoint for the study was progression-free survival (PFS) in patients with a PIK3CA mutation based on the investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The key secondary endpoint was overall survival (OS) for patients with a PIK3CA mutation. Other secondary endpoints included PFS and OS for patients without a PIK3CA mutation, overall response rate (ORR) and clinical benefit rate (CBR) for patients with and without a PIK3CA mutation.

Table 14.1 Summary of patient demographics and baseline disease characteristics in the PIK3CA-mutant cohort in SOLAR-1 (Full Analysis Set)

Demographic and disease characteristic variable	**Alpelisib + fulvestrant N=169 n (%)**	**Placebo + fulvestrant N=172 n (%)**	**All Patients N=341 n (%)**
Age (years)			
Median (Range)	63.0 (25 – 87)	64.0 (38 – 92)	63.0 (25 – 92)
Age category (years)			
18 to < 65	95 (56.2)	89 (51.7)	184 (54.0)
≥ 65	74 (43.8)	83 (48.3)	157 (46.0)
Sex			

Demographic and disease characteristic variable	Alpelisib + fulvestrant N=169 n (%)	Placebo + fulvestrant N=172 n (%)	All Patients N=341 n (%)
Female	168 (99.4)	172 (100)	340 (99.7)
Male	1 (0.6)	0	1 (0.3)
Race			
White	117 (69.2)	109 (63.4)	226 (66.3)
Asian	34 (20.1)	40 (23.3)	74 (21.7)
Black or African American	1 (0.6)	3 (1.7)	4 (1.2)
Other	8 (4.7)	10 (5.8)	18 (5.3)
ECOG performance status			
0	112 (66.3)	113 (65.7)	225 (66.0)
1	56 (33.1)	58 (33.7)	114 (33.4)
Missing	1 (0.6)	1 (0.6)	2 (0.6)
Stratum at randomisation			
Presence of lung and/or liver metastases	84 (49.7)	86 (50.0)	170 (49.9)
Prior CDK4/6 inhibitor	9 (5.3)	11 (6.4)	20 (5.9)
Last prior hormonal therapy			
Aromatase inhibitors	165 (97.6)	168 (97.7)	333 (97.7)
Anti-oestrogen therapy	25 (14.8)	29 (16.9)	54 (15.8)
Setting at last hormonal therapy			
Adjuvant	88 (52.1)	89 (51.7)	177 (51.9)
Therapeutic (Metastatic)	80 (47.3)	83 (48.3)	163 (47.8)
Endocrine resistance			
Primary[1]	23 (13.6)	22 (12.8)	45 (13.2)
Secondary[2]	120 (71.0)	127 (73.8)	247 (72.4)

Last hormonal therapy refers to hormonal medication received in the last regimen
Primary and secondary resistance as per ESMO definition
[1]Relapse < 24 months while on endocrine therapy (ET) in adjuvant setting or progression < 6 months while on ET in metastatic setting
[2]Relapse ≥ 24 months while on ET in adjuvant setting or relapse <12 months after end of ET in adjuvant setting or progression ≥ 6 months while on ET in metastatic setting

Of the 341 patients in the PIK3CA mutation cohort, overall demographics and baseline disease

characteristics, ECOG (Eastern Cooperative Oncology Group) performance status, tumour burden, and prior antineoplastic therapy were generally well balanced between the study arms (see Table 14.1). At baseline, 98% of patients had stage IV disease and 69% had < 3 metastatic sites. The majority of patients (74%) had bone metastases with or without other metastases at baseline, 23% having only bone metastases and 50% having liver/lung metastases.

The majority of patients (98%) received prior hormonal therapy as the last treatment (48% metastatic setting, 52% adjuvant setting), and 6% had previously been treated with a CDK4/6 inhibitor. Primary endocrine resistance, defined as relapsed within 24 months on adjuvant endocrine therapy or progression within 6 months on endocrine therapy for advanced disease, was observed in 13% of patients and secondary endocrine resistance, defined as relapsed after 24 months on adjuvant endocrine therapy, relapsed within 12 months of the end of adjuvant endocrine therapy, or progression after 6 months on endocrine therapy for advanced disease, was observed in 72% of patients.

Study Results

Primary analysis

The study met its primary objective at the final PFS analysis (data cut-off date 12-Jun-2018) demonstrating a statistically significant improvement in PFS by investigator assessment in the PIK3CA mutant cohort for patients receiving PIQRAY plus fulvestrant, compared to patients receiving placebo plus fulvestrant. There was an estimated 35% risk reduction of disease progression or death in favor of treatment with PIQRAY plus fulvestrant. The median PFS was 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm and 11.0 months (95% CI: 7.5, 14.5) in the PIQRAY plus fulvestrant arm (HR=0.65; 95% CI: 0.50, 0.85; one-sided p-value = 0.00065) (see Table 14-2 and Figure 14-1).

PFS results were supported by the results from a blinded independent review committee (BIRC) assessment in a randomly selected subset of approximately 50% of the patients in this cohort. Results were consistent across subgroups including stratification factors, major demographics, previous therapy and other prognostic factors, such as lung/liver metastases and bone lesions only (Figure 14-2).

A PFS benefit was not demonstrated in the cohort of patients without a PIK3CA mutation (HR = 0.85; 95% CI: 0.58, 1.25, one-sided p-value = 0.21). Therefore, PIQRAY is not indicated for use in this patient population.

At the time of final PFS analysis, overall survival was not mature with 92 (27%) deaths reported. The pre-specified O'Brien-Fleming stopping boundary was not crossed at the first interim OS analysis (see Table 14-2).

Efficacy results are summarized in Table 14-2, Figure 14-1 and 14-2.

Table 14-2 Summary of primary analysis efficacy results based on RECIST 1.1 criteria, in the

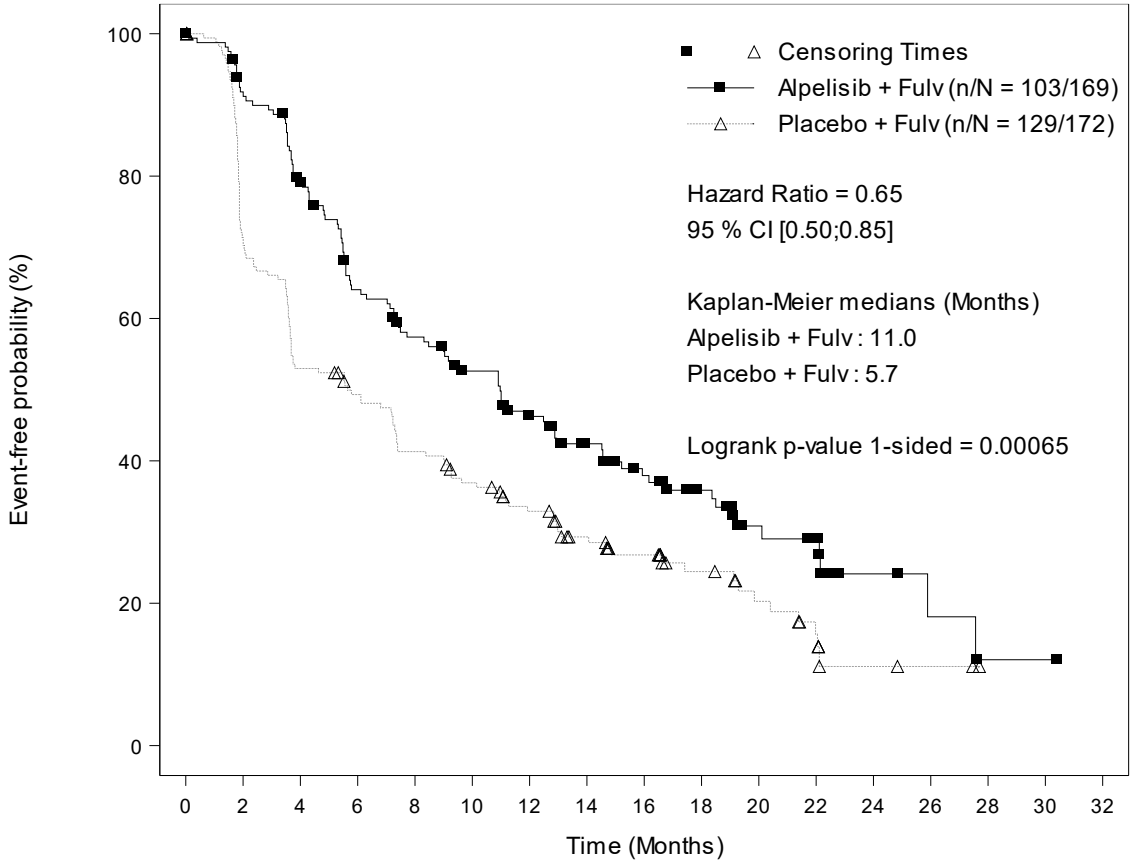
cohort of patients with PIK3CA mutation, per investigator assessment in SOLAR-1

	PIQRAY plus fulvestrant	Placebo plus fulvestrant
	N = 169	**N = 172**
Primary endpoint		
Progression-free survival		
Number of PFS events – n (%)	103 (60.9)	129 (75.0)
Progressive disease	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Median PFS – months (95% CI)	11.0 (7.5, 14.5)	5.7 (3.7, 7.4)
Hazard ratio (95% CI) [1]	0.65 (0.50, 0.85)	
One-sided p-value[1]	0.00065	
Secondary endpoints		
Overall Response Rate		
Full analysis set	**N = 169**	**N= 172**
ORR[3] (95% CI)	26.6 (20.1, 34.0)	12.8 (8.2, 18.7)
CBR[4] (95% CI)	61.5 (53.8, 68.9)	45.3 (37.8, 53.1)
Patients with measurable disease at baseline	**N = 126**	**N = 136**
ORR[3] (95% CI)	35.7 (27.4, 44.7)	16.2 (10.4, 23.5)

[1] Both log-rank test and Cox proportional hazards model are stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases. P-value from log-rank test was compared to pre-specified Haybittle-Peto stopping boundary (one-sided $p \leq 0.0199$).
[2]ORR (Overall Response Rate) = percentage of patients with confirmed Complete Response or Partial Response
[3]CBR (Clinical Benefit Rate) = proportion of patients with confirmed Complete Response or Partial Response, or Stable Disease or Non-Complete Response/Non-Progression Disease ≥ 24 weeks

Figure 14-1 Kaplan-Meier Progression Free Survival (PFS) curve in the cohort of patients with

PIK3CA mutation per local investigator assessment in SOLAR-1 (Primary Analysis)

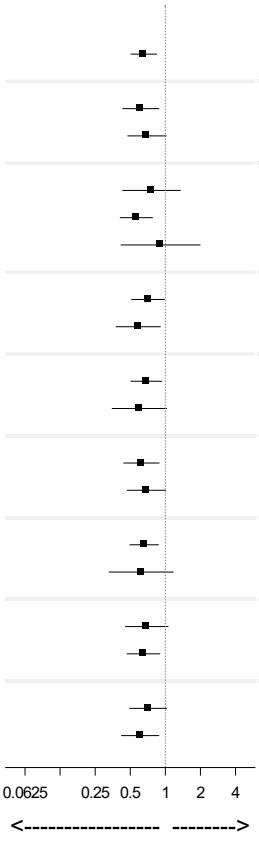


Number of subjects still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Alpelisib + Fulv	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo + Fulv	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

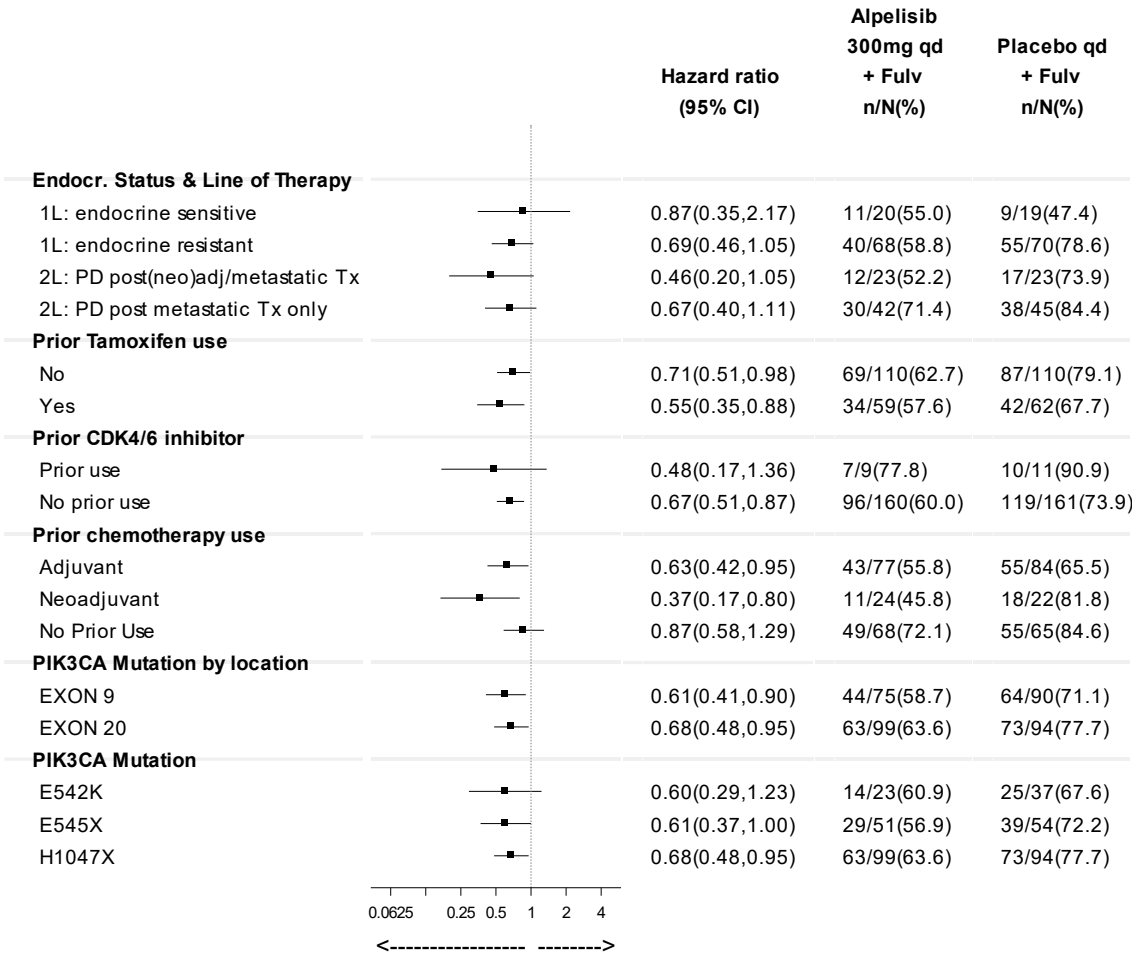
Figure 14-2 Forest plot of PFS based on investigator review in the cohort of patients with PIK3CA

mutation in SOLAR-1 (Primary Analysis)



	Hazard ratio (95% CI)	Alpelisib 300mg qd + Fulv n/N(%)	Placebo qd + Fulv n/N(%)
All subjects	0.65(0.50,0.85)	103/169(60.9)	129/172(75.0)
Age (years)			
< 65 Years	0.62(0.43,0.89)	58/95(61.1)	64/89(71.9)
>= 65 Years	0.70(0.47,1.03)	45/74(60.8)	65/83(78.3)
Race			
Asian	0.76(0.43,1.35)	21/34(61.8)	31/40(77.5)
White	0.56(0.41,0.78)	69/117(59.0)	80/109(73.4)
Other	0.91(0.41,2.00)	12/17(70.6)	17/20(85.0)
ECOG performance status			
0	0.71(0.51,0.99)	67/112(59.8)	79/113(69.9)
1	0.58(0.38,0.91)	36/56(64.3)	49/58(84.5)
Estr. & Progest. receptor status			
Both positive	0.69(0.50,0.94)	67/118(56.8)	99/132(75.0)
Positive Negative	0.60(0.35,1.03)	33/46(71.7)	28/38(73.7)
Lung and/or Liver metastases			
Present	0.62(0.44,0.89)	53/84(63.1)	72/86(83.7)
Absent	0.69(0.47,1.01)	50/85(58.8)	57/86(66.3)
Bone lesions only			
No	0.66(0.49,0.88)	85/127(66.9)	108/137(78.8)
Yes	0.62(0.33,1.18)	18/42(42.9)	21/35(60.0)
Visceral disease			
No	0.69(0.45,1.06)	41/76(53.9)	45/72(62.5)
Yes	0.65(0.47,0.90)	62/93(66.7)	84/100(84.0)
Line of adv. anti-cancer trt			
First Line	0.71(0.49,1.03)	51/88(58.0)	64/89(71.9)
Second Line	0.61(0.42,0.89)	50/79(63.3)	65/82(79.3)

Alpelisib better Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI



X denotes multiple amino acid changes possible; E545X (E545A, E545D, E545G, E545K), H1047X (H1047Y, H1047R, H1047L)

Final OS analysis

At the final OS analysis (data cut-off date of 23-Apr-2020), the study did not meet its key secondary objective. Median OS was 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm and 39.3 months (95% CI: 34.1, 44.9) in the Piqray plus fulvestrant arm [HR = 0.86 (95% CI 0.64, 1.15); one-sided p-value = 0.15 not statistically significant]. Final OS results are summarized in Table 14-3.

Table 14-3 – Final OS results in the cohort of patients with PIK3CA mutation in SOLAR-1

	PIQRAY plus fulvestrant	Placebo plus fulvestrant
	N = 169	N = 172
Secondary endpoint		
Overall survival		
Number of OS events – n (%)	87 (51.5)	94 (54.7)
Median OS – months (95% CI)	39.3 (34.1, 44.9)	31.4 (26.8, 41.3)
Hazard ratio (95% CI)[1]	0.86 (0.64, 1.15)	
One-sided p-value[2]	p= 0.15	

[1] Both log-rank test and Cox proportional hazards model are stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases.
[2] P-value was compared to prespecified O'Brien-Fleming efficacy boundary (one-sided p ≤ 0.0161) and was not significant.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

Alpelisib was evaluated in safety pharmacology, single- and repeated dose toxicity, genotoxicity and photo-toxicity studies.

General toxicology

Repeat dose-toxicity studies revealed that the majority of the observed alpelisib effects were related to the pharmacological activity of alpelisib as a p110α specific inhibitor of the PI3K pathway, such as the influence on the glucose homeostasis resulting in hyperglycemia and the risk of increased blood pressure.

Bone marrow and hematopoietic and lymphopoietic organs, pancreas, reproductive organs of both genders and mucosal tissues of the alimentary tract were the main target organs for adverse effects, which were generally reversible upon cessation of treatment. In exploratory rat studies, evidence of T-cell activation inducing inflammatory changes of the skin was observed.

Genotoxicity

Alpelisib was not mutagenic in a *bacterial reverse mutation (Ames)*, or aneugenic or clastogenic in human cell micronucleus and chromosome aberration tests *in vitro*, and it was not genotoxic in an *in vivo* rat micronucleus test.

Carcinogenicity

In the two-year oral carcinogenicity study in male and female Crl:WI(Han) rats, alpelisib was administered by oral gavage at doses of 1, 2, or 4 mg/kg/day for at least 104 weeks. The high dose of 4 mg/kg/day, selected based on a predicted maximum tolerated dose, corresponded to 0.2 times the AUC in patients at the recommended daily dose of 300 mg. Alpelisib was not carcinogenic in this study.

Reproductive and developmental toxicity

Embryo-foetal development studies

In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses of alpelisib up to 30 mg/kg/day, during the period of organogenesis.

In rats, oral administration of alpelisib was associated with maternal body weight loss or stagnation, low food consumption and embryonal death at 30 mg/kg/day, at approximately 3.2 times (based on AUC) the exposure in humans at the highest recommended dose of 300 mg. Low maternal body weight gain, increased incidences of enlarged brain ventricle in the foetuses, reduced foetal weight, decreased bone ossification and increased incidences of skeletal malformations were seen at 10 mg/kg/day, which is equal to approximately 0.9 times below the exposure in humans at the highest recommended dose.

In rabbits, at doses of ≥ 25 mg/kg/day, maternal body weight loss with reduced food intake was observed. At 15 mg/kg/day, slight transient body weight loss was observed. At ≥ 15 mg/kg/day, increased embryo-foetal deaths and malformations were observed, mostly related to the tail and head, and were associated with increased serum glucose levels in dams. At 25 mg/kg/day, reduced mean foetal weight was observed. The dose of 15 mg/kg/day dose in rabbits is equivalent to approximately 5.5 times (based on AUC) the exposure achieved at the highest recommended human dose.

Fertility studies

In repeated-dose toxicity studies up to 13 weeks duration, adverse effects were observed in reproductive organs of females and males, including vaginal atrophy and oestrus cycle variations in rats at doses ≥ 6 mg/kg/day (approximately 0.5 times the exposure in humans at the recommended dose of 300 mg/day based on AUC), and prostate atrophy in dogs at doses ≥ 15 mg/kg/day (approximately 2.8 times the exposure in humans at the recommended dose of 300 mg/day based on AUC). In general, the observed effects were reversible upon treatment discontinuation.

In two fertility studies, male rats were treated for 12-14 weeks (mated with untreated females) and females for about 5 weeks (mated with untreated males), similar effects on fertility were observed. In females at doses of 20 mg/kg/day (approximately 2 times the estimated exposure (based on AUC) in humans at the recommended dose of 300 mg), increased pre- and post-implantation losses led to reduced numbers of implantation sites and live embryos. The NOAEL (No-observed-adverse-effect-level) for female fertility was determined at 10 mg/kg/day (at exposure levels (based on AUC) at or below the recommended human dose of 300 mg). In males, at doses of ≥ 10 mg/kg/day, accessory glands weights (seminal vesicles, prostate) were reduced and correlated microscopically with atrophy and/or reduced secretion in prostate and seminal vesicles, respectively. Male fertility parameters were unaffected at doses up to 20 mg/kg/day.

Toxicokinetic endpoints were not included in either of the two fertility studies since the toxicokinetic parameters of alpelisib in rats had been sufficiently established earlier.

Juvenile Toxicity

No juvenile toxicity studies have been conducted.

Special toxicology

Phototoxicity

An *in vitro* phototoxicity test on the mouse Balb/c 3T3 fibroblast cell line did not identify a relevant phototoxicity potential for alpelisib.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]PIQRAY®

alpelisib tablets

This Patient Medication Information is written for the person who will be taking **PIQRAY®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **PIQRAY**, talk to a healthcare professional.

Your breast cancer will be treated with PIQRAY in combination with another drug called fulvestrant. Read the Patient Medication Information leaflets for the other drug as well as this one.

Serious warnings and precautions box

PIQRAY can cause:

- **Serious allergic reactions** (anaphylactic reactions) like face swelling, trouble breathing, flushing, rash, fever, or fast heart rate.
- **Serious skin reactions**
  - **Stevens-Johnson syndrome (SJS)** (a type of severe skin rash)
  - **Drug reaction with eosinophilia and systemic symptoms (DRESS)** a type of severe skin reaction that may affect one or more organs
  - **Erythema multiforme (EM)** (an allergic skin reaction)
- **High levels of:** blood acids (**diabetic ketoacidosis**), blood sugar (**hyperglycemia**) and its complications (**hyperglycemic hyperosmolar non-ketotic syndrome [HHNKS]**). Ketoacidosis can cause death.
  - You will have regular blood tests done before and during treatment with PIQRAY to determine your blood sugar levels which may require treatment.
  - Your healthcare professional may give you another medicine to help lower the side effects of high blood sugar or to lower the risk of it.
- **Lung problems** (**pneumonitis**): an inflammation of lung tissue.

The symptoms are listed in the 'Serious side effects and what to do about them' table. It is found later in this leaflet.

What PIQRAY is used for:

PIQRAY is used to treat breast cancer, which has spread to other parts of the body, in post-menopausal women and in men. The breast cancer must be hormone receptor-positive and with a specific gene mutation (PIK3CA). PIQRAY is used:

- with another drug for breast cancer called fulvestrant. This is used when the cancer gets worse after other therapies.

How PIQRAY works:
Alpelisib, the medicinal ingredient in PIQRAY, is a type of drug called a kinase inhibitor. It works by stopping certain cancer cells from dividing and growing. When given together with fulvestrant, PIQRAY may slow down the growth and spread of certain breast cancer cells.

The ingredients in PIQRAY are:
Medicinal ingredients: alpelisib
Non-medicinal ingredients: hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate, iron oxide black, iron oxide red, macrogol / polyethylene glycol (PEG), talc, titanium dioxide.

PIQRAY comes in the following dosage form:
Tablets, 50 mg, 150 mg and 200 mg

Do not use PIQRAY if:
- you are allergic to alpelisib or to any of the other ingredients in this drug or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PIQRAY. Talk about any health conditions or problems you may have, including if you:
- have or ever had diabetes or if you are pre-diabetic (high blood sugar levels)
- have or ever had serious skin problems like:
    - Stevens-Johnson syndrome (SJS), a type of severe skin rash
    - Drug reaction with eosinophilia and systemic symptoms (DRESS), a type of serious skin reaction that may affect one or more organs
    - Erythema multiforme (EM), allergic skin reaction
- have or ever had osteonecrosis of the jaw (exposed jaw bone)

Other warnings you should know about:

PIQRAY can cause serious side effects including:
- **Severe diarrhea, nausea and vomiting**: Your healthcare professional will monitor your health. They might give you medicine to treat these symptoms.
- **Colitis**, which is when your colon (large intestine) becomes inflamed. If you experience abdominal pain and mucous or blood in your stool, you may have colitis. Contact your healthcare professional as soon as possible.
- **Osteonecrosis of the jaw** (exposed jaw bone): PIQRAY can cause osteonecrosis of the jaw. You might have a dental check-up before starting your treatment to determine your jaw health.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Pregnancy and breast-feeding:
Female patients
- Do not use PIQRAY if you are pregnant or if you are still able to get pregnant and are not using highly effective birth control.

- Use highly effective birth control if you can get pregnant while taking PIQRAY and for at least 1 week after your last dose.
- Avoid becoming pregnant while taking PIQRAY. It may harm your unborn baby.
- Tell your health professional right away if you become pregnant or think you are pregnant during treatment with PIQRAY.
- If you can get pregnant, your health provider should do a pregnancy test before you start treatment with PIQRAY.
- It is not known if PIQRAY passes into breast milk. Do not breastfeed during treatment with PIQRAY and for at least 1 week after the final dose. Talk to your health professional about the best way to feed your baby during this time.

Male patients
- Use highly effective birth control while you are on PIQRAY and for at least 1 week after your last dose if:
  - your partner is pregnant, might be pregnant or can get pregnant
- Do not donate or store semen while you are on PIQRAY and for at least 1 week after your last dose.

Fertility – Male and Female patients: PIQRAY may affect your ability to have a child in the future.

Other patient groups:
- **Children under 18 years old** should not be given PIQRAY.
- **Adults 65 years and older** might get more certain side effects:
  - diarrhea, nausea, weight loss, shortness of breath, low potassium and high blood sugar levels.
- **Asians** might get more certain side effects:
  - severe skin and allergic reactions, rash.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PIQRAY:
- eltrombopag - used to treat low blood platelet count
- lapatinib - used to treat certain types of breast cancers
- pantoprazole - used to reduce the amount of acid produced in your stomach or heart burn
- ranitidine – used to treat heartburn
- cyclosporine – used to prevent organ transplant rejection
- warfarin - used to treat blood clots
- medicines called strong CYP3A4 inducers, including but not limited to:
  - rifampin - used to treat lung disease
  - apalutamide, enzalutamide and mitotane – used to treat types of cancer
  - carbamazepine and phenytoin – used to treat seizures
  - St. John's wort – an herbal remedy often used to treat depression
- medicines that can increase QT interval (a heart rhythm condition) including, but not limited to:
  - ondansetron – used to prevent nausea and vomiting
  - erythromycin, clarithromycin, azithromycin, moxifloxacin, levofloxacin, ciprofloxacin – used to treat bacterial infections (antibiotics)
- medicines used to treat diabetes. Always follow your healthcare professional's instructions on how to take these medicines with PIQRAY.

Ask your health professional if you are not sure whether your drug is listed above.

Tell your health professional if you are prescribed any new drugs during PIQRAY treatment.

How to take PIQRAY:

- Take PIQRAY only under the care of a doctor who knows how to use anti-cancer drugs.
- Take PIQRAY exactly as your healthcare professional tells you. Another drug called fulvestrant is also given to you while you are taking PIQRAY.
- Take PIQRAY once a day, at the same time, immediately following food.
- Swallow PIQRAY tablets whole. Do not chew, crush or split the tablets.
- Do not take PIQRAY tablets that are broken, cracked or look damaged.
- If you vomit after taking a dose of PIQRAY, do not take another dose on that day. Take your next dose at your regular time.
- Do not take more than the recommended dose prescribed by your healthcare professional.
- Do not change the PIQRAY dose or schedule unless your healthcare professional tells you to.
- Your healthcare professional will monitor your health. They may reduce, interrupt, or stop your PIQRAY dose. This may occur based on your current health, if you take certain other medications, or if you have certain side effects.

Usual dose:
Recommended daily dose
Adults:

- **300 mg starting dose**: Two 150 mg tablets once daily

Reduced recommended daily dose
Adults:

- **250 mg daily dose**: One 200 mg tablet and one 50 mg tablet, once daily
- **200 mg daily dose**: One 200 mg tablet once daily

Overdose:

If you think you, or a person you are caring for, have taken too much PIQRAY, contact a health professional, hospital emergency department or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

Show the PIQRAY packet. Medical treatment may be necessary.

Missed dose:

- If you are less than 9 hours late, take the missed dose, after food, as soon as you remember. Take the next dose at your regular time.
- If you are more than 9 hours late, skip the dose for that day. Wait until the regular time for your next dose.
- Do not take two doses to make up for a missed dose.

Possible side effects from using PIQRAY:
These are not all the possible side effects you may feel when taking PIQRAY. If you experience any side effects not listed here, contact your healthcare professional.

- Headache
- Tiredness, difficulty to sleep
- Changes in the way food tastes
- Decreased appetite
- Indigestion
- Toothache, gum pain
- Cracked, chapped lips
- Dry, cracked skin
- Blurred vision, dry eyes
- Muscle pain
- Hair loss

PIQRAY can cause abnormal blood test results. Your health professional will order some tests before and during your treatment. These include blood tests to monitor the blood sugar level and electrolytes (potassium, calcium) in your body. More frequent blood tests might be needed. Your health professional will tell you if your test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very Common			
Acute Kidney Injury (severe kidney problems): urinating less than usual or a lower amount of urine than usual, swelling in legs, ankles, and around the eyes, tiredness, confusion, nausea, seizure, chest pain			√
Anemia: (low levels of red blood cells): tiredness, weakness, fatigue, pale skin	√		
Gastrointestinal disorders: diarrhea, nausea, vomiting, stomach pain, decreased appetite, heartburn, swelling or bloating of the abdomen, indigestion	√		
Hyperglycemia (high blood sugar): increased thirst, frequent urination, larger amounts of urine, increased appetite with weight loss		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Hypertension (high blood pressure): headache, fatigue, dizziness, tinnitus, cold swelling, nosebleed, racing pulse or heart palpitations, shortness of breath	√		
Hypokalaemia (low levels of potassium in blood): muscle weakness and spasms, irregular heartbeats	√		
Stomatitis (mouth sores, inflammation of the mouth) or **Mucosal Inflammation** (inflammation of the moist body surfaces): red, sore or swollen mouth, lips, gums	√		
Urinary Tract Infection (infection in the urinary system): painful and frequent urination, pelvic pain, strong smelling urine, cloudy urine		√	
Common			
Dehydration (when there is not enough water in the body): thirst; reduced sweating and urine; dry mouth	√		
Erythema Multiforme (allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the centre, possibly with mild itching or burning; possibly swollen lips			√
Hypocalcaemia (low levels of calcium in blood): cramps	√		
Ketoacidosis (high level of acids in the blood): difficulty breathing, nausea, vomiting			√
Lymphopenia (low white blood cells): fever; cough; runny nose; enlarged lymph nodes; painful joints; rash; night sweats; weight loss	√		
Osteonecrosis of the Jaw (exposed jaw bone): pain, swelling, numbness or heavy feeling of the jaw, or loosening of a tooth		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Palmar-plantar erythrodysaesthesia syndrome (also called Hand-Foot Syndrome: reddening and/or swelling, peeling on the palms and soles, tingling sensation and burning pain of the feet		√	
Non-infectious Pneumonitis and Pneumonia (lung inflammation): new or changing respiratory problems including difficult or painful breathing, cough, rapid breathing, pain in chest while breathing, blue discoloration of the lips, tongue or skin, or hiccups			√
Serious Allergic Reactions: rash with red bumps, fever, itching, general swelling (including face), shortness of breath, irregular heartbeat			√
Thrombocytopenia (low platelet count): spontaneous bleeding or bruising		√	
Uncommon			
Pancreatitis (inflamed pancreas): severe upper stomach pain			√
Stevens Johnson Syndrome or erythema multiforme (EM), or toxic epidermal necrolysis (TEN): (severe skin reaction): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by hives fever, chills, headache, cough, body aches or swollen glands			√
Unknown			
Angioedema (a type of hypersensitivity reaction where the tissue under the skin swells)**:** swollen face, throat, hands, feet or genitals; difficult breathing			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Colitis (inflammation of your intestine)**:** diarrhea, severe abdominal pain, stool with mucus or blood			√
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect more than one or more organs): fever, severe rash, swollen lymph glands, flu-like feeling, swelling of the face; possibly yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinate less often, less urine			√
Hyperglycemic Hyperosmolar non-ketotic Syndrome (HHNKS, a complication of high blood sugar): Confusion, dry mouth, dry or flushed skin, nausea, vomiting, tiredness, need to pass urine frequently, thirst.			√
Uveitis (inflammation of the uvea, the layer beneath the white of the eyeball): redness of the eye, eye pain, sensitivity to light, dark floaters in your field of vision, blurred vision, decrease in vision, small pupil.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your health professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Do not store above 30°C.
- Do not take this medicine after the expiry date, which is stated on the box.
- Keep in the original package. Protect from moisture.
- Keep out of reach and sight of children.

Ask your pharmacist how to dispose of medicines you no longer use.

If you want more information about PIQRAY:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.novartis.ca), or by calling 1-800-363-8883.

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