Drug Monograph

A - Drug Name

alpelisib

COMMON TRADE NAME(S): Piqray®

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B - Mechanism of Action and Pharmacokinetics

Alpelisib is an inhibitor of phosphatidylinositol 3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. The PI3K signaling pathway plays a role in various biological processes, including proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis. Mutations in the gene encoding the catalytic α-subunit of PI3K (PI3KCA) leads to activation of PI3Kα and Akt-signaling, cellular transformation, and tumour generation. In breast cancer cell lines, alpelisib inhibits the phosphorylation of PI3K downstream targets, including Akt, and shows activity in cell lines harbouring a PIK3CA mutation. When compared with either agent alone, the combination of alpelisib with fulvestrant has synergistic antitumor activity in PIK3CA-mutated, estrogen receptor-positive models.

Absorption	Time to reach steady state	3 days
	Peak plasma levels	2-4 hours
	Effects with food	Co-administration of alpelisib, with a high-fat high-calorie meal increased AUC by 73% and Cmax by 84%, and co-administration with a low-fat low-calorie meal increased AUC by 77% and Cmax by 145%
Distribution	PPB	89%

Metabolism	Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite and to a lesser extent by CYP3A4.	
	Inactive metabolites	Yes
Elimination	Half-life	~ 9 hours
	Feces	81% (36% as unchanged drug)
	Urine	14% (2% as unchanged drug)

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C - Indications and Status

Health Canada Approvals:

- Breast cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 10% of patients and with ≥ 2% higher incidence in the alpelisib arm in a phase III study of fulvestrant with alpelisib or placebo, in patients with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (9%) (may be severe)	E
Dermatological	Alopecia (20%)	E
	Dry skin (18%)	E
	Erythema multiforme (1%)	E D
	Rash, pruritus (52%) (may be severe)	E D
	Stevens-Johnson syndrome (<1%)	E D
	Toxic epidermal necrolysis (rare)	E D
Gastrointestinal	Abdominal pain (17%)	E
	Anorexia, weight loss (36%)	E
	Colitis (rare)	E D L
	Diarrhea (58%) (may be severe)	E D L
	Dyspepsia (11%)	E
	Mucositis (30%)	E
	Nausea, vomiting (45%)	E
General	Edema (15%)	E
	Fatigue (42%)	E
	Fever (14%)	E
	Mucosal dryness (19%) (or inflammation)	E
Hematological	Anemia (10%)	E
	Myelosuppression (5%)	E
Hepatobiliary	↑ LFTs (10%) (may be severe)	E
	Pancreatitis (<1%)	E
Hypersensitivity	DRESS syndrome (rare)	E D
	Hypersensitivity (4%) (may be severe)	I E
Infection	Infection (10%) (UTI)	E
Metabolic / Endocrine	Hyperglycemia (65%) (37% severe) (including ketoacidosis <1%, hyperglycemic hyperosmolar non-ketotic syndrome (rare))	E D L
Musculoskeletal	Osteonecrosis of jaw (4%) (2% severe)	D
Nervous System	Dysgeusia (18%)	E
	Headache (18%)	E
Ophthalmic	Blurred vision , dry eyes (5%)	E

Renal	Creatinine increased (10%)	E
	Other (5%) - Acute Kidney Injury	E
Respiratory	Pneumonitis (2%) (may be severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for alpelisib include hyperglycemia, diarrhea, rash, pruritus, nausea, vomiting, fatigue, anorexia, weight loss, mucositis, alopecia, mucosal dryness/inflammation and dry skin.

Severe **hyperglycemia has been reported,** including hyperglycemic hyperosmolar non-ketotic syndrome and fatal cases of diabetic ketoacidosis. Among patients who experienced ≥ grade 2 hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range: 5 to 517 days). Patients with type I or uncontrolled type II diabetes were excluded from the phase 3 trial. The median duration of ≥ grade 2 hyperglycemia was 10 days. Median time to improvement from the first event for patients with ≥ grade 2 hyperglycemia with at least 1 grade improvement was 8 days. All who continued fulvestrant but discontinued alpelisib (due to hyperglycemia) had fasting plasma glucose (FPG) levels that returned to baseline. Patients with pre-diabetes, diabetes, BMI ≥ 30, elevated FPG or HbA1c ≥ ULN, or age ≥ 75 years have a higher risk of developing severe hyperglycemia and/or associated complications (e.g. ketoacidosis).

Severe **diarrhea**, including dehydration and acute kidney injury have been reported. Among patients with grade ≥ 2 diarrhea, the median time to onset was 46 days (range: 1 to 442 days). **Colitis** has also been reported during post marketing.

Serious **hypersensitivity** reactions, including anaphylactic reaction and anaphylactic shock have been reported. Symptoms include, but are not limited to, dyspnea, flushing, rash, fever or tachycardia. Hypersensitivity and anaphylactic reactions were more common in Asian patients compared to other races. **Angioedema** has also been reported during post marketing.

Cases of osteonecrosis of the jaw (ONJ) have been reported. All patients experiencing ONJ were exposed to prior or concomitant bisphosphonates or denosumab.

Severe **cutaneous adverse reactions**, including **SJS**, **EM**, and **DRESS**, have been reported. The median time to first onset of ≥ grade 2 rash was 12 days (range: 2 to 220 days).

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Alpelisib is only for use in hormone receptor (HR) positive, HER2-negative advanced breast cancer patients with known a PIK3CA mutation confirmed using a validated test.

Fasting plasma glucose and/or HbA1c (hemoglobin A1c test) should be performed and glucose levels should be corrected in patients with abnormal fasting glucose levels in the range of prediabetic or diabetic before initiating treatment.

A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with risk factors for ONJ, such as invasive dental procedures, concomitant therapies, poor oral hygiene and comorbid disorders.

Other Supportive Care:

- Oral antihistamine administration may be considered prophylactically for rash and severe cutaneous reactions to decrease incidence and severity, at the time of treatment initiation.

Adults:

Combination:

Oral: 300 mg Daily

Dosage with Toxicity:

Dose Level	Alpelisib Dose (mg/day)
0	300
-1	250
-2	200
-3	Discontinue

Dose Modifications:

Toxicity	Grade	Action
Fasting glucose	Grade 1 (> ULN - 8.9 mmol/L)	No dosage adjustment required.†
	Grade 2 (> 8.9 - 13.9 mmol/L)	No dosage adjustment required.† If fasting glucose does not decrease to ≤ 8.9 mmol/L in ≤ 21 days, ↓ alpelisib by 1 dose level.
	Grade 3 (> 13.9 - 27.8 mmol/L)	Hold.† Consider additional antidiabetic medications* for 1-2 days until hyperglycemia improves. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). If fasting glucose decreases to ≤ 8.9 mmol/L in ≤ 3-5 days, resume at 1 dose level ↓. If fasting glucose does not decrease to ≤8.9 mmol/L within: • 3 to 5 days: consultation with a clinician with expertise in the treatment of hyperglycemia is recommended. • 21 days following appropriate treatment: discontinue.
	Grade 4 (≥ 27.8 mmol/L)	Hold.† Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). Re-check fasting glucose within 24 hours and as clinically indicated. If fasting glucose decreases to ≤ 27.8 mmol/L, follow specific recommendations for hyperglycemia above. If fasting glucose is confirmed at > 27.8 mmol/L, discontinue.

	Rash and cutaneous reactions** (excluding severe cutaneous adverse reactions etiology)	Grade 1 (< 10% body surface area (BSA) with active skin toxicity)	No dosage adjustment required; initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment. If active rash does not improve within 28 days of appropriate treatment, add low dose oral corticosteroid.
		Grade 2 (10% - 30% BSA with active skin toxicity)	No dosage adjustment required; initiate/intensify topical corticosteroid and oral antihistamine treatment. Consider adding low dose systemic corticosteroid. If rash improves to ≤ grade 1 within 10 days, discontinue systemic corticosteroids.
		Grade 3 (> 30% BSA with active skin toxicity; severe rash not responsive to medical management)	Hold and initiate or intensify topical/oral corticosteroid and antihistamine treatment. When resolved to ≤ grade 1, resume at 1 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)	Discontinue
	Severe cutaneous adverse reactions, including Stevens-Johnson Syndrome /Toxic Epidermal Necrolysis, DRESS or erythema multiforme	Any	Discontinue
	Diarrhea or Colitis	Grade 1	No dosage adjustment required.†
		Grade 2	Hold until resolved to ≤ grade 1 then resume at same dose level.†

		If it recurs, hold until ≤ grade 1 then resume at 1 dose level ↓.†
	Grade 3	Hold until resolution to ≤ grade 1 then resume at 1 dose level ↓.†
	Grade 4	Discontinue
Pancreatitis	Grade 2 or 3	Hold until resolved to ≤ grade 1 then resume at 1 dose level ↓. If toxicity re-occurs, discontinue.
	Grade 4	Discontinue
Symptoms of pneumonitis	Any	Hold and investigate; discontinue if confirmed
Bilirubin	Grade 2	Hold until resolved to ≤ grade 1: • if improved within 14 days, resume at same dose. • if improved in >14 days, resume at 1 dose level ↓.
	Grade 3	Hold until resolution to ≤ grade 1 then resume at 1 dose level ↓.
	Grade 4	Discontinue
Serious hypersensitivity reactions / Anaphylactic reactions	Any	Discontinue
All other toxicities	Grade 1 or 2	No dosage adjustment required.†
	Grade 3	Hold until resolved to ≤ grade 1 then resume at 1 dose level ↓.
	Grade 4	Discontinue.

†Initiate or intensify appropriate medical therapy (e.g. oral anti-diabetic or anti-diarrhea treatment) and monitor as clinically indicated. For Grade 2 or 3 colitis, consider additional treatment, such as steroids.

*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 dose interruption.

**For all grades of rash, consider consultation with a dermatologist.

Dosage with Hepatic Impairment:

Hepatic Impairment	Alpelisib Dose
Child-Pugh Class A, B or C	No dose adjustment required

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Alpelisib Dose
≥ 30	No dose adjustment required
< 30	Effect on alpelisib pharmacokinetics is unknown

Dosage in the elderly:

No dose adjustment is required as no overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients; however, gastrointestinal toxicity (primarily diarrhea and nausea), hyperglycemia, weight loss, hypokalemia and dyspnea were reported more frequently in older patients.

Dosage based on ethnicity:

No dose adjustment is required; however, rash, severe cutaneous reactions, hypersensitivity and anaphylactic reaction, and pancreatitis were more frequently reported in Asian patients compared to Caucasian patients.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

- Alpelisib should be administered once daily at approximately the same time each day immediately following a meal.
- 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.
- If a dose 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 and the next dose should be taken at its usual time. Missed doses should not be made up the next day.
- If a dose is vomited, do not administer an additional dose on that day; resume the dosing schedule the next day at the usual time.
- Do not store above 30°C.
- Store in the original package to protect from moisture.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to alpelisib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Other Warnings/Precautions:

- Caution should be exercised when alpelisib and drugs known to cause ONJ are used either simultaneously, or sequentially. Alpelisib treatment should not be initiated in patients with ongoing ONJ.
- Do not initiate alpelisib treatment in patients with history of severe cutaneous reactions.
- Alpelisib is associated with QT prolongation. Exercise caution if alpelisib is used concomitantly with medicinal products that are known to prolong the QTc interval. Patients with uncontrolled heart disease and/or recent cardiac events (including long QT syndrome, QTcF > 450 ms for males or > 460 ms for females) were excluded from the phase III clinical study.
- The safety of alpelisib in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the phase III clinical study. Patients with pre-diabetes, diabetes, BMI ≥ 30, elevated FPG or HbA1c $\geq$ ULN, or age ≥ 75 years have a higher risk of developing severe hyperglycemia and/or associated complications (e.g. ketoacidosis).
- It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Other Drug Properties:

- Phototoxicity: No

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Genotoxicity: No
- Teratogenicity: Documented in animals
- Embryotoxicity: Documented in animals
    - Alpelisib is not recommended for use in pregnancy.
    - Adequate contraception should be used by patients and their partners during treatment, and for at least **1 week** after the last dose.
    - Patients should not donate or store semen during treatment and for at least **1 week** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **1 week** after the last dose.
- Fertility effects: Probable
  Based on animal studies, adverse effects were observed in reproductive organs of males and females, including vaginal atrophy and oestrus cycle variations.

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H - 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) and a substrate for BCRP transporter.

No dose adjustment is required when administering alpelisib with CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and P-gp substrates.

Alpelisib has been shown to have no effect on fulvestrant exposure (and vice-versa).

Alpelisib can be co-administered with acid reducing agents since it should be taken with food. Food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value.

Caution should be exercised when alpelisib and drugs known to cause ONJ are used either simultaneously, or sequentially.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ alpelisib concentration and/or efficacy	↑ metabolism of alpelisib	Avoid co-administration with strong CYP3A4 inducers
BCRP inhibitors (e.g. cyclosporine, eltrombopag, lapatinib)	↑ alpelisib concentration and/or toxicity	↑ alpelisib drug uptake	Avoid co-administration with BCRP inhibitors. If concomitant use is unavoidable, closely monitor for increased alpelisib adverse reactions
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Caution. Perform additional ECG monitoring as clinically indicated.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and as clinically indicated
Fasting glucose	Baseline and at least weekly for the first 2 weeks of treatment, followed by every 4 weeks and as clinically indicated. Monitor more frequently for the first few weeks in patients with pre-diabetes, diabetes, BMI ≥ 30, or age ≥ 75 years
Fasting glucose (if patient experiences hyperglycemia after initiating alpelisib)	Regularly, at least until fasting glucose decreases to normal levels. During treatment with antidiabetic medications, monitor at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated
HbA1c	Baseline, every 3 months and as clinically indicated
ECG	Baseline and as clinically indicated. More frequently if taken concomitantly with medications known to prolong the QTc interval
Liver function tests	Baseline and as clinically indicated
Electrolytes, including potassium and calcium	Baseline and in patients experiencing gastrointestinal toxicity as clinically indicated
Clinical toxicity assessment for edema, fatigue, fever/infection, ONJ, pancreatitis, dysgeusia, pneumonitis, hypersensitivity, renal, dermatological and gastrointestinal effects (including mucositis)	As clinically indicated

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

André F, et al.; SOLAR-1 Study Group. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019 May 16;380(20):1929-1940.

Prescribing information: Piqray® (alpelisib). Novartis Pharmaceuticals Corporation. July 2021.

Product Monograph: Alpelisib (Piqray®). Novartis Pharmaceuticals Canada Inc., November 1, 2023.

June 2024 Updated Interactions section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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