Drug Monograph

A - Drug Name

abemaciclib

COMMON TRADE NAME(S): Verzenio®

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B - Mechanism of Action and Pharmacokinetics

Abemaciclib inhibits cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). It blocks retinoblastoma tumor suppressor protein phosphorylation and prevents progression through the cell cycle, resulting in arrest at the G1 phase, leading to suppression of tumour growth.

Absorption	Bioavailability	45% (following a single 200 mg oral dose)
	Effects with food	Cmax increased by 26%; AUC increased by 9%, after a high-fat, high-calorie meal
	Time to reach steady state	5 days (following repeated twice daily dosing)
	Peak plasma levels	8 hours
Distribution	PPB	96-98%
	Cross blood brain barrier?	Yes
Metabolism	Active metabolites	Yes
	Inactive metabolites	Yes

Elimination	Feces	81%, mainly as metabolites
	Urine	3%
	Half-life	24.8 hours

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C - Indications and Status

Health Canada Approvals:

- Breast cancer (HR positive, HER2 negative)

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

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table contains adverse effects from a phase III trial of early breast cancer patients (monarchE) where the incidences in patients receiving abemaciclib in combo with endocrine therapy were ≥2% more than endocrine therapy alone . Adverse effects from the advanced breast cancer clinical trial (Monarch 3) with abemaciclib in combination with anastrozole or letrozole are marked with "†". Severe adverse events from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Cardiotoxicity (rare)	E
	Hypotension (rare)	E
	Venous thromboembolism (2%)	E
Dermatological	Alopecia (10%) (≤ Grade 2)	E
	Dry skin (10%) †	E
	Hand-foot syndrome (rare)	E
	Nail disorder (5%)	D
	Rash, pruritus (10%)	E

Gastrointestinal	Anorexia, weight loss (12%)	E
	Constipation (10%)	E
	Diarrhea (83%) (8% severe)	E
	Dry mouth (5%) †	E
	Dyspepsia (8%)	E
	Mucositis (13%)	E
	Nausea, vomiting (29%) (Generally mild)	E
General	Edema - limbs (10%) †	E
	Fall (6%) †	E
	Fatigue (39%)	E
	Flu-like symptoms (12%) †	E
	Other - Lymphedema (10%)	E
Hematological	Myelosuppression (45%) (19% severe, including febrile neutropenia ≤1%)	E D
Hepatobiliary	↑ LFTs (10%) (severe 2%)	E D
Hypersensitivity	Hypersensitivity (rare)	E
Infection	Infection (48%) (severe 4%)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (9%) † (↓ PO4, ↓ K, ↓ Ca)	E
Musculoskeletal	Musculoskeletal pain (21%)	E
Nervous System	Dizziness (10%)	E
	Dysgeusia (5%)	E
	Headache (18%)	E
Ophthalmic	Dry eye (5%)	E
	Watering eyes (5%) †	E
Renal	Creatinine increased (21%) †	E
	Nephrotoxicity (rare)	I E
Respiratory	Cough, dyspnea (15%) †	E
	Pneumonitis (5%)	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 abemaciclib include diarrhea, infection, myelosuppression, fatigue, nausea/vomiting, creatinine increased, musculoskeletal pain, headache, cough/dyspnea and mucositis.

Diarrhea is the most common adverse reaction across clinical studies with a higher incidence during the initial month of treatment. Grade 3 diarrhea has occurred but Grade 4 has not been reported. Diarrhea had been associated with dehydration and infection. The median time to onset of the first diarrhea event was 6 to 8 days and the median duration of grade 2 and 3 diarrhea was 9 to 11 days and 6 to 8 days, respectively.

Myelosuppression was reported in patients receiving abemaciclib. Grade 3 or higher neutropenia has been observed with both monotherapy and combination therapy. The median time to first episode of neutropenia (≥ grade 3) was 29 to 37 days and the median duration of ≥ grade 3 neutropenia was 12 to 15 days. Febrile neutropenia has occurred rarely, and deaths due to neutropenic sepsis have been observed.

Venous thromboembolism (VTE), including deep vein thrombosis (DVT), pulmonary embolism, pelvic venous thrombosis, cerebral venous thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis have been reported in up to 6% of patients. Deaths due to VTE have occurred.

Hepatotoxicity and **increases in ALT** have been reported including Grade 3 or higher events. The median time to onset of ≥ grade 3 ALT elevation was 57 to 87 days and the median time to resolution (to < grade 3) was 13-14 days.

Severe, life threatening and fatal **interstitial lung disease (ILD)/pneumonitis** has been reported with abemaciclib. Across clinical trials, 3.2% of patients had ILD/pneumonitis of any grade with 0.4% of patients experiencing ≥ grade 3 ILD. The median time to onset was 8.2 months.

A higher rate of **infections** was reported in patients who received abemaciclib plus endocrine therapy compared to patients treated with placebo plus endocrine therapy. Infections were also reported in patients on single agent abemaciclib. Fatal cases were reported in clinical trials.

Abemaciclib may increase **serum creatinine,** without affecting glomerular function, by inhibiting renal tubular secretion transporters. It was observed within the first month of abemaciclib clinical trials. Serum creatinine levels remained elevated but stable during treatment, and were reversible at treatment discontinuation. Consider alternative markers that are not based on creatinine (e.g. BUN) for determining renal function.

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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.

Adults:

Monotherapy:

Oral: 200 mg BID

In combination with endocrine therapy*:

Oral: 150 mg BID

*Pre/perimenopausal women, and men treated with abemaciclib AND an aromatase inhibitor, tamoxifen, or fulvestrant should be treated with a gonadotropin releasing hormone (GnRH) agonist, according to local clinical practice.

Dosage with Toxicity:

Dose Level	Abemaciclib Dose (mg BID)	
	Combination with Endocrine Therapy	Single Agent
0	150	200
-1	100	150
-2	50	100
-3	Discontinue	50
-4	Not applicable	Discontinue

Toxicity	Grade	Action
Hematologic*	Grade 3	Hold until ≤ grade 2; resume at same dose.
	Grade 4 or recurrent grade 3	Hold until ≤ grade 2; resume at 1 dose level ↓.
Diarrhea**	Grade 2	If no resolution to ≤ grade 1 within 24 hours, hold until resolution; resume at same dose.
	Grade 2 that persists/recurs after resumption at the same dose (despite maximal supportive measures)	Hold until ≤ grade 1; resume at 1 dose level ↓.
	≥ Grade 3 or requires hospitalization	
Interstitial lung disease (ILD)/ Pneumonitis	Persistent or recurrent grade 2 toxicity that does not resolve to baseline or grade 1 within 7 days (despite maximal supportive measures)	Hold until recovery to baseline or ≤ grade 1; resume at 1 dose level ↓.
	Grade 3 or 4	Discontinue
Hepatotoxicity	Persistent or recurrent grade 2, or grade 3 (ALT, AST >5 to 20 times ULN), WITHOUT increase in total bilirubin >2 times ULN	Hold until recovery to baseline or grade 1; resume at 1 dose level ↓.
	AST and/or ALT >3 times ULN with total bilirubin >2 times ULN (in the absence of cholestasis)	Discontinue
	Grade 4 (ALT, AST >20 times ULN)	Discontinue
Venous thromboembolism	Grade 1 or 2	**Early breast cancer:** Hold; restart when patient is stable and if clinically appropriate **Metastatic breast cancer:** No dose modification required
	Grade 3 or 4	**For early or metastatic breast cancer:** Hold; restart when patient is stable and if clinically appropriate

All other non-hematologic toxicities	Persistent or recurrent grade 2 toxicity that does not resolve to baseline or grade 1 within 7 days (despite maximal supportive measures)	Hold until recovery to baseline or ≤ grade 1; resume at 1 dose level ↓.
	Grade 3 or 4	

*If blood cell growth factors are required, hold abemaciclib for at least 48 hours after the last growth factor dose and until toxicity resolves to ≤ grade 2; resume at the next lower dose (unless already reduced due to the toxicity that required the growth factor). Growth factor use is as per current local guidelines.

**At the first sign of loose stools, begin management with antidiarrheal agents (i.e. loperamide) and increase oral fluid intake.

Dosage with Hepatic Impairment:

Hepatic Impairment	Abemaciclib Dose
Mild or moderate impairment (Child-Pugh class A or B)	No dosage adjustment necessary.
Severe impairment (Child-Pugh class C)	Reduce abemaciclib frequency to once daily.

Dosage with Renal Impairment:

Renal Impairment	Abemaciclib Dose
Mild or Moderate (CrCl ≥ 30 mL/min)	No dosage adjustment necessary.
Severe (CrCl < 30 mL/min); ESRD	Has not been studied

Dosage in the elderly:

No dosage adjustment is required. No overall differences in safety or efficacy between patients ≥ 65 years of age and younger. Patients ≥65 years of age reported more hematologic adverse events, hypokalemia (including grade 3), hypocalcemia, grade ≥3 infections, decreased appetite, and increased blood creatinine compared to younger patients in a subgroup analysis from clinical studies.

Dosage based on ethnicity:

No dose adjustment based on race is required. Higher incidences of increased ALT and AST and neutropenia have been reported in East Asian patients compared to Caucasian patients in clinical trials.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Abemaciclib tablets should be swallowed whole (do not chew, crush, or split tablets before swallowing). Tablets should not be ingested if they are not intact.
- Abemaciclib doses may be taken with or without food and should be administered at approximately the same times every day.
- Avoid fruit or juice from grapefruit, Seville oranges or starfruit.
- Abemaciclib tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- If a dose is missed or vomited, the next dose should be taken at the scheduled time. The patient should not take 2 doses at the same time to make up for the missed dose.
- Store at room temperature (15°C to 30°C).

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

Other Warnings/Precautions:

- There are no data regarding abemaciclib safety or efficacy in patients with prior exposure to other CDK 4/6 inhibitors.

Other Drug Properties:

- Carcinogenicity:
  No data

Pregnancy and Lactation:

- Genotoxicity: Unlikely
  Not observed in animal studies
- Teratogenicity: Yes
- Embryotoxicity: Yes
  Observed in animal studies.
  Abemaciclib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **3 weeks** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **3 weeks** after the last dose.
- Fertility effects: Probable
  Abemaciclib may impair fertility in males.

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H - Interactions

Abemaciclib inhibits the renal transporters organic cation transporter 2 (OCT2), multidrug and extrusion toxin protein (MATE1), and MATE2.

In vitro, abemaciclib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong or moderate CYP3A inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ abemaciclib concentration and/or toxicity	↓ metabolism of abemaciclib	Avoid co-administration with strong CYP3A inhibitors. Use caution when co-administered with moderate CYP3A inhibitors. If co-administration with a CYP3A inhibitor is unavoidable, reduce abemaciclib dose to 50 mg twice daily when combined with strong or moderate CYP3A inhibitors. When combined with ketoconazole, abemaciclib dose should be reduced to 50 mg once daily. When combined with clarithromycin, diltiazem or verapamil, abemaciclib dose should be reduced to 100 mg twice daily. If the CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose used before starting the inhibitor.
Weak CYP3A inhibitors (e.g. ranitidine)	↑ abemaciclib concentration and/or toxicity	↓ metabolism of abemaciclib	Use with caution. If co-administration with a weak CYP3A inhibitor is unavoidable, reduce

			abemaciclib dose to 100 mg twice daily. If the CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose used before starting the inhibitor.
CYP3A inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ abemaciclib concentration and/or efficacy	↑ metabolism of abemaciclib	Avoid co-administration with strong CYP3A inducers. Consider alternative agents with less CYP3A induction. Use with caution when co-administered with moderate or weak CYP3A inducers.
OCT2, MATE1, MATE2 substrates (i.e. metformin)	↑ substrate concentration and/or toxicity	↓ substrate renal clearance and secretion	Caution

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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, every two weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
Liver function tests	Baseline, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
Renal function tests*	Baseline and as clinically indicated
Clinical toxicity assessment for signs and symptoms of venous thrombosis, infections, gastrointestinal, respiratory, dermatologic effects and fatigue	At each visit

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

*Abemaciclib may increase serum creatinine, without affecting glomerular function, by inhibiting renal tubular secretion transporters. Consider alternative markers that are not based on creatinine (e.g. BUN) for determining renal function.

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Electrolytes (including calcium)	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- abemaciclib - For the adjuvant treatment, in combination with endocrine therapy, of adult patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of disease recurrence, according to criteria

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K - References

Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. Clin Cancer Res. 2017;23(17):5218-24.

Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol. 2017 Nov 10;35(32):3638-46.

Johnston SRD, Harbeck N, Hegg R. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-98.

Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol. 2017;35:2875-84.

Verzenio (abemaciclib) product monograph. Toronto, Ontario: Eli Lilly Canada Inc., January 2022.

February 2025 Updated Supplementary Public Funding 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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