DRUG NAME: Abemaciclib

SYNONYM(S): LY2835219[1]

COMMON TRADE NAME(S): VERZENIO®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Abemaciclib is an orally administered, selective, reversible small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. CDK 4/6 form complexes with cyclin D to promote phosphorylation of retinoblastoma (Rb) protein, which allows cell cycle progression. Abemaciclib is cell cycle phase-specific, blocking transition from the G1 to the S phase by binding to CDK 4/6 to inhibit Rb protein phosphorylation. Abemaciclib is an immunosuppressive agent.[2-5]

PHARMACOKINETICS:

Oral Absorption	absolute bioavailability = 45%; median T_{max} 8 hours (4.1 – 24 hours)	
Distribution	highly bound to serum albumin and alpha-1 acid glycoprotein	
	cross blood brain barrier?	yes
	volume of distribution[2]	747 L
	plasma protein binding	96-98%
Metabolism	extensive hepatic metabolism primarily via CYP 3A4	
	active metabolite(s)	major: N-desethylabemaciclib (M2); minor: hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18)
	inactive metabolite(s)	M1 (oxidative metabolite)
Excretion	primarily as metabolites in feces	
	urine	3%
	feces	81%
	terminal half life[2]	24.8 h
	clearance[2]	21.8 L/h

Adapted from standard reference [1,2,6] unless specified otherwise.

USES:

Primary uses:
*Breast cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- abemaciclib dose reduction may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway[7]

Developed: 1 May 2020
Revised: 1 January 2024

Special populations:
- ***East Asian patients*** may experience a higher frequency of adverse events compared with Caucasian patients[2]
- ***patients aged 65 years or older*** may experience more hematologic adverse events, hypokalemia, hypocalcemia, and severe infections compared to younger patients[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Abemaciclib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2,6]

Fertility: In animal studies, hypospermia and atrophy/degeneration/necrosis of the testis, epididymis, prostate and seminal vesicle were observed in male test subjects at doses up to two times that used in humans. No effects on female reproductive organs were observed.[2,6]

Pregnancy: In animal studies, abemaciclib was teratogenic when administered during organogenesis at maternal exposures approximately equal to the expected human exposure following recommended doses. Findings included decreased fetal body weights and an increased incidence of cardiovascular and skeletal malformations and variations. For women of childbearing potential, pregnancy testing is recommended prior to initiating treatment. Contraception should be used during treatment and for at least three weeks after the last dose.[2,6]

Breastfeeding is not recommended due to the potential secretion into breast milk. Do not breastfeed during treatment and for at least three weeks after the last dose.[2,6]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[8,9] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. **Incidence data in the Side Effects table is based on abemaciclib monotherapy data where possible. Incidence data based on combination therapy is indicated with an asterisk (*).**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (25%, severe 5%)
	febrile neutropenia (<1%)[10]
	leukopenia (17%, severe 5%)
	neutropenia (37%, severe 24%); median onset to first episode = 29 days, median duration = 15 days
	thrombocytopenia (21%, severe 4%)
cardiac	palpitations (3%)[11]
	sinus tachycardia (3%)[11]
eye	lacrimation increase (8%)
	dry eye (5%)
gastrointestinal	*emetogenic potential:* low[12]
	abdominal pain (39%, severe 2%)

Developed: 1 May 2020
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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	constipation (17%, severe <1%)
	diarrhea (90%, severe 20%): see paragraph following **Side Effects** table
	dry mouth (14%)
	dyspepsia (8%)
	flatulence (5%)
	gastroesophageal reflux disease (5%)
	nausea (64%, severe 5%)
	stomatitis (14%)
	vomiting (35%, severe 2%)
general disorders and administration site conditions	chills (6%)
	fatigue (65%, severe 13%)
	pain (20%, severe 2%)
	peripheral edema (8%)
	pyrexia (11%)
infections and infestations	***infections*** (31%, severe 7%)[6]; fatal events have been reported
	upper respiratory tract infection (8%, severe <1%)
	urinary tract infection (8%)
investigations	***ALT increase*** (7%, severe <1%); may require dose interruption/reduction/delay
	AST increase (8%, severe 2%); may require dose interruption/reduction/delay
	serum creatinine increase (13%, severe <1%); reversible, occurs during first 28 days of treatment
	weight decrease (14%)
metabolism and nutrition	appetite decrease (46%, severe 3%)
	dehydration (10%, severe 2%)
	hypokalemia (5%, severe 2%)
musculoskeletal and connective tissue	arthralgia (8%)
	back pain (11%, severe <1%)
	bone pain (7%, severe <1%)
	muscular weakness (7%, severe 2%)
	myalgia (5%)
	pain in extremity (5%)
nervous system	dizziness (11%)
	dysgeusia (12%)
	headache (21%)
	neuropathy (8%)

Developed: 1 May 2020
Revised: 1 January 2024

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
psychiatric	anxiety (5%)
	insomnia (5%)
respiratory, thoracic and mediastinal	cough (19%)
	dyspnea (14%, severe 3%)
	interstitial lung disease/pneumonitis* (2-5%, severe <1%); see paragraph following **Side Effects** table
	oropharyngeal pain (6%)
	rhinitis, allergic (5%)
	upper airway cough syndrome (5%)
renal and urinary	acute kidney injury (2%)[11]
	chronic kidney disease (2%)[11]
skin and subcutaneous tissue	alopecia (12%)
	dry skin (9%)
	pruritus (8%, severe <1%)
	rash (8%, severe 2%)
vascular	***venous thromboembolic events**** (5-6%, severe <1%); fatal events have been reported

Adapted from standard reference[2,6,10] unless specified otherwise.

Diarrhea is reported in 90% of patients receiving monotherapy with abemaciclib and has been associated with dehydration and infection. Incidence is greatest during the first month of therapy. Median onset of first diarrhea is 7 days. For grade 2 and 3 diarrhea, median duration is 8 and 5 days, respectively. In the majority of events, symptoms resolve with supportive treatment and/or dose reductions. Start antidiarrheal therapy at the first sign of loose stools. Treatment interruption and subsequent dose reduction is recommended for grade 3 or 4 diarrhea, and for diarrhea that requires hospitalization.[2,6]

Interstitial lung disease (ILD)/pneumonitis has been reported and can be life-threatening. Median time to onset is 8 months. Monitor patients for pulmonary symptoms which may include cough, dyspnea, hypoxia, or interstitial infiltrates on radiologic exam. Dose interruption and/or reduction is recommended for persistent or recurrent grade 2 ILD/pneumonitis. Permanently discontinue treatment for grade 3 or 4 ILD/pneumonitis.[1,2,13]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anastrozole, letrozole, exemestane[2,3]	no effect on abemaciclib pharmacokinetics		
clarithromycin[2,7]	2.2-fold increase in plasma exposure of abemaciclib and active metabolites	strong inhibition of CYP 3A4 by clarithromycin	avoid concurrent use; if coadministration cannot be avoided, reduce abemaciclib dose to 100 mg PO twice daily

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AGENT	EFFECT	MECHANISM	MANAGEMENT
diltiazem[7]	*predicted* 2.4-fold increase in AUC of abemaciclib and active metabolites	moderate inhibition of CYP 3A4 by diltiazem	monitor for abemaciclib toxicity; consider abemaciclib dose reduction to 100 mg PO twice daily
fulvestrant[2,3]	no effect on abemaciclib pharmacokinetics		
grapefruit juice[2]	may increase plasma level of abemaciclib	may inhibit CYP 3A4 metabolism of abemaciclib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of abemaciclib therapy
ketoconazole[3,6,7]	*predicted* 7.2-fold increase in AUC of abemaciclib and active metabolites	strong inhibition of CYP 3A4 by ketoconazole	avoid concurrent use; if coadministration cannot be avoided, reduce abemaciclib dose to 50 mg PO once daily
loperamide[2,3]	no effect on abemaciclib pharmacokinetics		
metformin[2,6]	37% increase in AUC and 22% increase in C_{max} of metformin	inhibition of OCT2, MATE1 and MATE2-K transporters by abemaciclib	clinical significance unknown; monitor blood glucose levels
rifampin[2]	77% decrease in AUC and 45% decrease in C_{max} of abemaciclib and active metabolites	strong induction of CYP 3A4 by rifampin	avoid concurrent use
verapamil[7]	*predicted* 1.6-fold increase in AUC of abemaciclib and active metabolites	moderate inhibition of CYP 3A4 by verapamil	monitor for abemaciclib toxicity; consider abemaciclib dose reduction to 100 mg PO twice daily

Abemaciclib is a ***substrate*** of CYP 3A4. CYP 3A4 ***inhibitors*** may increase the plasma concentration of abemaciclib. Monitor for abemaciclib toxicity when used concurrently. When coadministered with a *weak* CYP 3A4 inhibitor, consider abemaciclib dose reduction to 100 mg PO twice daily. When coadministered with a *moderate* CYP 3A4 inhibitor, consider abemaciclib dose reduction to 50 mg PO twice daily. Avoid concurrent use with *strong* CYP 3A4 inhibitors if possible. If coadministration with *strong* CYP 3A4 inhibitors cannot be avoided, reduce abemaciclib dose to 50 mg PO twice daily. If the CYP 3A4 inhibitor is discontinued, abemaciclib may be resumed at the prior dose after a washout period equal to 3-5 elimination half-lives of the inhibitor.[1-3,6,7,14]

CYP 3A inducers may decrease the plasma concentration of abemaciclib and its metabolites. Abemaciclib dose adjustment is not required for patients who require concomitant weak or moderate CYP 3A inducers. Avoid coadministration with ***strong CYP 3A inducers***.[2,6]
Abemaciclib inhibits Organic Cation Transporter 2 (***OCT2***) and Multidrug and Toxic Compound Extrusion Protein-1 and 2 (***MATE1 and MATE2-K***) transporters *in vitro*; clinical significance is unknown.[2,3]

Abemaciclib is a substrate and inhibitor of P-glycoprotein (***P-gp***) and Breast Cancer Resistance Protein (***BCRP***) *in vitro*; clinical significance is unknown.[2,3,6]

SUPPLY AND STORAGE:

Oral: Eli Lilly Canada Inc. supplies abemaciclib as 50 mg, 100 mg, 150 mg, and 200 mg film-coated tablets. Tablets contain lactose. Store at room temperature.[2]

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral[4,7,10,15-17]:	***150 mg*** (range 50 – 200 mg) ***PO twice daily**** Administer with food or on an empty stomach. Do not take with grapefruit or grapefruit juice. *dose adjustment may be required for some drug interactions
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	creatinine clearance ≥30 mL/min: no adjustment required[1,2] creatinine clearance <30 mL/min: no information found calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild/moderate impairment (Child-Pugh class A or B): no adjustment required[2,6] severe impairment (Child-Pugh class C): reduce dosing frequency to once daily[1,6]
Dosage in dialysis:	no information found

Children: safety and efficacy not established[2]

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Developed: 1 May 2020
Revised: 1 January 2024