DRUG NAME: Ribociclib

SYNONYM(S): LEE011[1]

COMMON TRADE NAME(S): KISQALI®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Ribociclib 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. Ribociclib 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. Ribociclib is an immunosuppressive agent.[2-4]

PHARMACOKINETICS:

Oral Absorption	time to peak: 1-4 h; steady state after 8 days	
Distribution	equally distributed between red blood cells and plasma	
	cross blood brain barrier?	unlikely (based on rat models)
	volume of distribution	1,090 L
	plasma protein binding	70%
Metabolism	extensive hepatic metabolism via CYP 3A4	
	active metabolite(s)	negligible
	inactive metabolite(s)	numerous, including M1, M4, M13
Excretion	mainly fecal elimination	
	urine	23% (12% parent drug, 4% M4)
	feces	69% (17% parent drug, 14% M4)
	terminal half life[3]	30-55 h
	clearance	26 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Breast cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- untreated congenital long QT syndrome or QTc ≥450 ms at baseline[2]

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Caution:

- ***QT interval prolongation*** has been reported; caution in patients with known risk factors. Correct preexisting electrolyte disturbances and monitor ECG and electrolytes. Administer ribociclib in the morning as QT prolongation risk may be increased when it is taken in the evening (due to bradycardia which naturally occurs during sleep).[2,5]
- ribociclib starting dose reduction may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test or in a mammalian *in vivo* mutation test.[2]

Fertility: In animal studies, seminiferous tubule degeneration and reduced luminal sperm were observed.[2]

Pregnancy: In animal studies, lower fetal weights and an increased incidence of fetal malformations and variants were observed. For females of reproductive potential, pregnancy testing is recommended prior to initiating treatment. Contraception should be used during treatment and for at least 21 days after the last dose of ribociclib.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women may begin breastfeeding 21 days after the last dose of ribociclib.[2]

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[6]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. **Incidence data based on combination therapy (instead of monotherapy) is indicated with an asterisk (*).**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (26-44%, severe 3-6%)[7-9]
	febrile neutropenia (12%, severe 12%)[8]
	leukopenia (43-100%, severe 17-82%)[7,8]
	lymphopenia (24-82%, severe 16-53%)[7,8]
	neutropenia (46-94%, severe 27-76%)[7,8]
	thrombocytopenia (30-71%, severe 8-28%)[7-9]
gastrointestinal	*emetogenic potential:* low[10]
	constipation (12%)[8]
	diarrhea (12-23%, severe 2%)[7,8]
	nausea (25-42%, severe 2%)[7,9]
	stomatitis* (10-12%, severe ≤1%)[2,3,11]
	vomiting (26-41%)[7,8]
	edema, peripheral* (5-15%, severe <1%)[2,11]
	fatigue (12-45%, severe 2-3%)[7-9]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	pyrexia (18%)[8]
hepatobiliary	***hepatotoxicity**** (2%, severe 2%); see paragraph following **Side Effects** table
infections and infestations	infection* (35-50%, severe 4%)[3,12]; see paragraph following **Side Effects** table
investigations	***ALT increase**** (12-46%, severe 5-10%)[2,11]; see paragraph following **Side Effects** table
	AST increase (16%, severe 3%)[9]; see paragraph following **Side Effects** table
	bilirubin increase* (1-5%, severe 1%)[2,3]; see paragraph following **Side Effects** table
	creatinine increase (11-41%)[7,8]
	gamma-glutamyltransferase increase* (5-52%, severe 2%)[3,11]
	QT interval prolongation (11-41%, severe 2-12%)[7,8]; see paragraph following **Side Effects** table
metabolism and nutrition	appetite decrease (10-19%, severe 3%)[7,9]
	hypocalcemia* (2-5%, severe 2%)[2,3]
	hypoglycemia* (23%)[3]
	hypokalemia* (11%)
	hypophosphatemia (12-13%, severe 6%)[8,9]
musculoskeletal and connective tissue	asthenia (13%)[9]
nervous system	syncope* (≤3%, severe 2%)[2,3]
respiratory, thoracic and mediastinal	interstitial lung disease/pneumonitis[13] (<1%; severe <1%); sometimes fatal
skin and subcutaneous tissue	alopecia* (19-33%)[2,3]
	pruritus* (9-20%, severe <1%)[2,3,11]
	rash* (13-23%, severe <1%)[2]
vascular	***pulmonary embolism**** (1%, severe 1%)

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Increases in ALT and/or AST have been reported. Grade 3/4 elevations mainly occur during the first six months of treatment and are usually reversible upon discontinuation of ribociclib. Rarely, transaminase elevations greater than three times the upper limit of normal (ULN) can occur together with bilirubin increases greater than two times the ULN with normal alkaline phosphatase levels and without cholestasis. Recovery to normal is expected after permanent discontinuation of ribociclib. Hepatotoxicity has also been reported, including hepatocellular injury and drug-induced liver injury. Monitor liver function tests at baseline and throughout treatment. Patients may require ribociclib dose reduction, interruption, or permanent discontinuation to manage hepatoxicity.[2]

Neutropenia is commonly reported and can occur from cycle 1 onward. The median time to first neutropenic episode is 16 days, with a median duration of 15 days for grade 3 or greater neutropenia.[2] Unlike neutropenia associated with traditional chemotherapy, neutropenia induced by ribociclib is reversible, noncumulative, and is not commonly associated with fever.[4] Ribociclib treatment may need to be interrupted, dose reduced, or discontinued for grade 3 or 4 neutropenia and/or infection.[2]

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QTc interval prolongation has been reported and has (rarely) lead to fatalities; avoid concurrent therapy with drugs that increase risk. For all patients, electrolyte and ECG monitoring is advised at baseline and at regular intervals. Maximal QT/QTc prolongation is expected during days 8-21 of a 28 day cycle. If the QTc interval increases to more than 480 ms, ribociclib should be held. Once the QTc interval resolves to 480 ms or less, ribociclib may be resumed, however, adjustment to a lower dose level may be required. Permanently discontinue ribociclib if torsades de pointes or signs of other serious arrhythmias occur.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[2]	may increase plasma level of ribociclib	may inhibit CYP 3A4 metabolism of ribociclib in the intestinal wall	avoid grapefruit and grapefruit juice for the duration of treatment with ribociclib
anastrozole, exemestane, letrozole[14]	no effect on ribociclib pharmacokinetics		
midazolam[2,14]	2.1 fold increase in C_{max} and 3.8 fold increase in AUC of midazolam	inhibition of CYP 3A4 by ribociclib	avoid concurrent administration
proton pump inhibitors, H2 blockers, antacids[14]	no effect on ribociclib absorption		
rifampin[2,14]	81% decrease in C_{max} and 89% decrease in AUC of ribociclib	strong induction of CYP 3A4 by rifampin	avoid concurrent administration
ritonavir[2,14]	1.7 fold increase in C_{max} and 3.2 fold increase in AUC of ribociclib	strong inhibition of CYP 3A4 by ritonavir	avoid concurrent administration

Ribociclib is a **substrate of CYP 3A**. Co-administration of ***strong CYP 3A inhibitors and inducers*** should be avoided to prevent increased or decreased ribociclib exposure, respectively. If co-administration with a strong CYP 3A inhibitor is unavoidable, reduce ribociclib dose to 200 mg once daily. If the strong inhibitor is discontinued, resume ribociclib at the dose used prior to the initiation of the inhibitor (after at least five half-lives of the inhibitor).[2]

Ribociclib is an **inhibitor of CYP 3A** *in vitro*. If possible, avoid co-administration of ribociclib with narrow therapeutic index ***CYP 3A substrates.*** If co-administration is unavoidable, dose reduction of the CYP 3A substrate may be required.[2]

Ribociclib may inhibit Breast Cancer Resistance Protein (BCRP), human Bile Salt Export Pump (BSEP), Organic Cation Transporter 2 (OCT2), and Multidrug and Toxic Compound Extrusion Protein-1 (MATE1) transporters *in vitro*; clinical significance is unknown.[2,14]

Ribociclib has been associated with ***QTc*** prolongation. Avoid concurrent therapy with drugs associated with QTc prolongation, torsades de pointes, bradycardia, and/or drugs that disrupt electrolyte levels. If concurrent use is unavoidable, monitor for toxicity.[2]

SUPPLY AND STORAGE:

Oral: Novartis supplies ribociclib 200 mg film-coated tablets as ribociclib succinate. Store at room temperature. Keep in original packaging to protect from moisture.[2]

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

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(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[2,15]*:*	Cycle Length: ***4 weeks***:	***600 mg PO once daily for 21 consecutive days starting on day 1**** Administer in the morning, with food or on an empty stomach. Swallow tablets whole; crushing or chewing tablets may lead to increased ribociclib exposure.[16] *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[2] creatinine clearance 15 to <30 mL/min: reduce initial dose to 200 mg once daily[3] creatinine clearance <15 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[2]*:*	mild impairment (Child-Pugh class A): no adjustment required moderate to severe impairment (Child-Pugh class B or C): reduce initial dose to 400 mg once daily	
Dosage in dialysis:	no information found	

Children: safety and efficacy not established[2]

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