Drug Monograph

A - Drug Name

ribociclib

COMMON TRADE NAME(S): Kisqali™

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B - Mechanism of Action and Pharmacokinetics

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb). Inhibition of pRb phosphorylation arrests the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth.

Absorption	Effects with food	No clinically significant effect
	Peak plasma levels	Achieved between 1 and 4 hours
	Time to reach steady state	8 days
Distribution	PPB	70%
	Distribution Sites	Equally distributed between red blood cells and plasma
	Cross blood brain barrier?	Relatively low brain penetration observed in animals with intact blood brain barriers.
Metabolism	• Ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4. • No major metabolite was considered to have clinically relevant contribution to efficacy and safety.	

	Active metabolites	No
	Inactive metabolites	Yes
Elimination	Ribociclib is eliminated mainly via the feces, with a small contribution from the renal route.	
	Half-life	32 hours
	Feces	69% (total dose); 17% unchanged
	Urine	23% (total dose); 12% unchanged

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C - Indications and Status

Health Canada Approvals:

- Breast cancer

(Includes conditional approvals)
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 adverse effects reported below were based on a phase III study of postmenopausal women with breast cancer, receiving ribociclib plus letrozole or placebo plus letrozole, where the incidence was ≥ 2% more than placebo. Severe or life-threatening adverse effects from other sources and post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	QT interval prolonged (5%) (< 1% severe)	E
	Venous thromboembolism (4%) (may be severe)	E

Dermatological	Alopecia (33%)	E
	Rash, pruritus (20%) (including TEN; may be severe)	I E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia, weight loss (19%)	E
	Constipation (25%)	E
	Diarrhea (35%)	E
	Dyspepsia (7%)	I E
	Mucositis (12%)	E
	Nausea, vomiting (52%)	I
General	Edema (15%)	E
	Fatigue (37%)	E
Hematological	Myelosuppression ± infection, bleeding (74%) (60% severe)	E
Hepatobiliary	↑ LFTs (18%) (10% severe; 2% hepatotoxicity)	D
Metabolic / Endocrine	Abnormal electrolyte(s) (5%) (↓ Ca, ↓ K, ↓ PO4; 4% severe)	E
Musculoskeletal	Musculoskeletal pain (20%)	E
Nervous System	Dysgeusia (9%)	E
	Headache (22%)	E
	Insomnia (12%)	E
	Syncope (3%) (2% severe)	E
Ophthalmic	Dry eye (6%)	E
	Watering eyes (7%)	E
Renal	Creatinine increased (7%) (< 1% severe)	E
Respiratory	Dyspnea (12%)	E
	Pneumonitis (rare) (may be severe)	E D

* "*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 ribociclib include myelosuppression ± infection, bleeding, nausea, vomiting, fatigue, diarrhea, alopecia, constipation, headache, musculoskeletal pain, rash, pruritus, anorexia and weight loss.

Neutropenia was the most frequently reported side effect in patients treated with ribociclib plus any combination. The median time to onset for Grade ≥ 2 neutropenia was 16 days, while the median time to resolution to Grade < 3 was 12 days.

Drug induced liver injury [ALT or AST > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN, without cholestasis] or **Hy's Law** has been reported with ribociclib combination therapy. In patients treated with ribociclib plus letrozole or fulvestrant, recovery to normal levels occurred within 154 days or within 121 to 532 days, respectively, after ribociclib discontinuation.

Median time to onset of **QTcF** > 480 msec was 15 days regardless of combination and these changes were reversible upon withholding the dose or modification.

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E - Dosing

Refer to protocol by which the patient is being treated.

Hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to starting or continuing ribociclib.

Ribociclib should be started only in patients with QTcF < 450 msec.

Pre- and perimenopausal women treated with ribociclib and an aromatase inhibitor or fulvestrant should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

Adults:

Oral: 600 mg/day on Days 1 to 21, q28 days

In combination with an aromatase inhibitor (e.g., letrozole) or fulvestrant. Refer to regimen monographs for dosing details.

Dosage with Toxicity:

Dose Level	Ribociclib Dose (mg/day) for 3 out of 4 weeks
0	600
-1	400
-2	200
-3	Discontinue

Toxicity	Severity		Ribociclib Dose
Neutropenia	Grade 3 (ANC 0.5 to <1 x 10^9/L)		Hold dose until ANC ≥ 1 x 10^9/L, then restart at the same dose level. If recurs, hold dose until ANC ≥ 1 x 10^9/L, then restart with 1 dose level ↓.
	Grade 4 (ANC <0.5 x 10^9/L) or febrile neutropenia		Hold dose until ANC ≥ 1 x 10^9/L, then restart with 1 dose level ↓.
QTcF	> 480 msec		Hold dose until QTcF resolves to ≤ 480 msec, then restart with 1 dose level ↓. If recurs, hold dose until QTcF resolves to ≤ 480 msec, then restart with 1 dose level ↓.
	> 500 msec		Hold dose until QTcF resolves to ≤ 480 msec, then restart with 1 dose level ↓.
Torsade de Pointes, or polymorphic ventricular tachycardia, unexplained syncope or Signs/symptoms of serious arrhythmia	Any		Discontinue.
Bilirubin ≤ 2 x ULN	and	AST and/or ALT >3 to 5 x ULN (Grade 2)	If Baseline Grade 2: continue at current dose. If Baseline Grade 0-1: hold dose until ≤ baseline, then restart at the same dose. If recurs, hold dose until ≤ baseline, then restart with 1 dose level ↓.
	and	AST and/or ALT >5 to 20 x	Hold dose until ≤ baseline, then restart with 1 dose level ↓.

		ULN (Grade 3)	If recurs, discontinue.
	and	AST and/or ALT >20 x ULN (Grade 4)	Discontinue.
Bilirubin > 2 x ULN, in the absence of cholestasis	and	AST and/or ALT >3 x ULN (Grade ≥ 2) irrespective of baseline	Discontinue.
Interstitial lung disease (ILD)/pneumonitis	Grade 2 (symptomatic)		Hold dose until recovery to Grade ≤ 1, then restart with 1 dose level ↓.
	Grade 3 or 4		Discontinue.
Severe cutaneous reactions (e.g. progressive widespread skin rash often with blisters or mucosal lesions)	Any		Discontinue.
Other related toxicity	Grade 3		Hold dose until Grade ≤ 1, then restart at same dose. If recurs, hold dose until Grade ≤ 1, then restart with 1 dose level ↓.
	Grade 4		Discontinue.

Dosage with Hepatic Impairment:

Ribociclib has not been studied in patients with moderate or severe hepatic impairment (ALT or AST ≥ 5 x ULN or total serum bilirubin ≥ ULN [except documented Gilbert's syndrome]).

Hepatic Impairment	Ribociclib Starting Dose
Mild (Child-Pugh class A)	No change
Moderate (Child-Pugh class B)	400 mg once daily; only if benefit outweighs risk
Severe (Child-Pugh class C)	400 mg once daily; only if benefit outweighs risk

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Ribociclib Starting Dose
≥ 30	No change.
15 to < 30	200 mg daily*; use only if benefit outweighs risk.
< 15	No data available.

*No data in breast cancer patients; data from healthy or non-cancer patients with severe renal impairment.

Dosage in the elderly:

No adjustment of the starting dose is required. No overall difference in safety was observed between patients over 65 years of age and younger patients.

Dosage based on gender:

No clinically relevant effects of gender on ribociclib pharmacokinetics parameters.

Dosage based on ethnicity:

No clinically relevant effects of race on ribociclib pharmacokinetics parameters.

Children:

The safety and efficacy of ribociclib in pediatric patients has not been established.

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F - Administration Guidelines

- Administer ribociclib with or without food, approximately at the same time each day, preferably in the morning.
- Tablets should be swallowed whole and not chewed, crushed or split prior to swallowing. Tablets that are broken, cracked, or otherwise not intact should not be ingested.
- If the patient vomits after taking ribociclib, do not give an extra dose; give the next dose at the usual time.
- If a dose is missed, it should be skipped and the next dose taken at the usual time, the next day. Patients should not take extra doses to make up for a missed dose.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during ribociclib treatment.
- Ribociclib should be stored at room temperature (below 30°C) and in the original package to protect from moisture.

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G - Special Precautions

Contraindications:

- Patients with hypersensitivity to this drug or to any ingredient in the formulation.
- Patients with untreated congenital long QT syndrome, a QTcF interval of ≥ 450 msec at baseline, and those who are at significant risk of developing QTc prolongation (for example, uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmia).

Other Warnings/Precautions:

- Ribociclib is associated with concentration-dependent QTc prolongation, with expected maximal QTc prolongation during steady state treatment between days 8 and 21 of the 28-day cycle.
- Exercise caution in patients who are suspected to be at an increased risk of Torsades de Pointes during treatment with a QT-prolonging drug.
- Avoid use in patients with uncorrected hypokalemia, hypomagnesemia, or hypocalcemia and other risk factors.
- Use in caution in patients at risk of thromboembolic events.
- Patients should exercise caution when driving or operating machinery due to fatigue or syncope.

Other Drug Properties:

- Carcinogenicity: Unknown
- Phototoxicity: Unlikely

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Genotoxicity: No
- Teratogenicity: Yes
  Ribociclib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **21 days** after the last dose (for females) and **6 months** after the last dose (general recommendation for males).
- Excretion into breast milk: Probable
  Breastfeeding is not recommended during treatment or for at least **21 days** after the last dose. Ribociclib is excreted into milk in animals.
- Fertility effects: Probable
  Animal data suggests that ribociclib may affect male fertility.

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H - Interactions

- Ribociclib is primarily metabolized by CYP3A4. Therefore, medicinal products which can influence CYP3A4 enzyme activity may alter the pharmacokinetics of ribociclib and ribociclib can affect the pharmacokinetics of co-administered CYP3A substrates. Ribociclib has weak inhibitory effects on CYP1A2 substrates though no induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 was observed *in vitro*.
- Ribociclib may inhibit BCRP, OCT2, Multidrug and Toxic Compound Extrusion Protein-1 (MATE1) and human Bile Salt Export Puup (BSEP). Monitor patients closely when co-administering ribociclib and substrates of these transporters.
- There is no clinically relevant interaction with letrozole, exemestane, anastrozole or fulvestrant.
- There is no expected interaction with goserelin.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, pomegranate, Seville oranges or starfruit)	↑ ribociclib exposure	↓ metabolism of ribociclib	Avoid strong CYP3A4 inhibitors. If unavoidable, ↓ ribociclib dose to 200mg. After discontinuation of strong CYP3A4 inhibitor, resume ribociclib dose used prior to initiating the CYP3A4 inhibitor (after a washout period of at least 5 half-lives). Monitor closely.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ ribociclib exposure	↑ metabolism of ribociclib	Avoid strong CYP3A4 inducers.
CYP3A4 substrates with narrow therapeutic index (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, midazolam, pimozide, quinidine, sirolimus and tacrolimus)	↑ CYP3A4 Substrate exposure	↓ metabolism of CYP3A4 Substrate	Avoid CYP3A4 substrates with a narrow therapeutic index. If unavoidable, consider reducing dose of substrate.
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone,	↑ risk of QT prolongation	Additive	Avoid to the extent possible.

chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)			
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	serum electrolyte imbalance	↓ electrolyte levels	Avoid to the extent possible.
Drugs that reduce heart rate (i.e. beta blockers, calcium channel blockers, digoxin)	↑ risk of arrhythmia		Avoid to the extent possible.
Tamoxifen	↑ risk of QT prolongation	↑ tamoxifen exposure by 2-fold with co-administration	Combined use is not recommended.

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically indicated
Liver function tests	Baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically indicated (more frequent monitoring required in patients with ≥ Grade 2 LFTs)

Electrolytes, including potassium, magnesium, calcium, and phosphorous	Baseline, at regular intervals during steady-state treatment in later cycles and as clinically indicated (for example, patients with QTc prolongation)
ECG	Baseline, repeat on day 14 of cycle 1, at the beginning of cycle 2, at regular intervals thereafter (at approximately day 14 of the cycle) and as clinically indicated (more frequent monitoring in patients at risk)
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment of infection, bleeding, thromboembolism (close monitoring in patients at risk), pneumonitis, gastrointestinal and skin effects, and fatigue	At each visit

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- ribociclib - For the treatment of patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER 2)-negative, unresectable locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant according to clinical criteria

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K - References

Hortobagyi, G. N. et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. New Engl. J. Med. 375, 1738–1748 (2016).

Product monograph: Kasqali (ribociclib). Novartis Pharmaceuticals. December 22, 2020.

April 2021 Updated indications, adverse effects, dosing, administration, special precautions, interactions and monitoring sections

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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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