Regimen Monograph

A - Regimen Name

LETRRIBO Regimen

Letrozole - Ribociclib

Disease Site	Breast
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For the treatment of estrogen-receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer: • As first-line therapy for unresectable locally advanced or metastatic disease, OR • As second-line therapy after progression on a chemotherapy for unresectable locally advanced or metastatic disease (Refer to EAP funding criteria details.)
Supplementary Public Funding	**ribociclib** Exceptional Access Program (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) (EAP Website)

letrozole
ODB - General Benefit (letrozole) (ODB Formulary)

back to top

B - Drug Regimen

letrozole	2.5 mg	PO	Daily
ribociclib	600 mg	PO	Days 1 to 21

Note: Pre- or perimenopausal women should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

back to top

C - Cycle Frequency

Letrozole: Continuous

Ribociclib: Every 28 days (3 weeks on, 1 week off)

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Also refer to CCO Antiemetic Recommendations.

Other Supportive Care:

- Assess patient's risk factors for osteoporosis and consider calcium and vitamin D supplements and bisphosphonates where appropriate. Refer patients to the Bone Health During Cancer Treatment pamphlet for more information.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

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

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

Dosage with toxicity

Dose Level	Ribociclib Dose (mg/day) for 3 out of 4 weeks	Letrozole Dose (mg/day) continuous
0	600	2.5
-1	400	2.5
-2	200	2.5
-3	Discontinue	2.5

Letrozole: No dosage adjustment necessary for hematological and/or non-hematological toxicities.

Ribociclib:

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 ULN (Grade 3)	Hold dose until ≤ baseline, then restart with 1 dose level ↓. 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	Any		Discontinue.

lesions)		
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.

Hepatic Impairment

Hepatic Impairment	Ribociclib Starting Dose	Letrozole Dose
Mild (Child-Pugh class A)	No dosage adjustment needed.	No dosage adjustment needed, although exposure may ↑ by 37%.
Moderate (Child-Pugh class B)	400 mg once daily; only if benefit outweighs risk	
Severe (Child-Pugh class C)		No data. Monitor closely and consider dose modification.

Renal Impairment

Creatinine Clearance (mL/min)	Ribociclib Starting Dose	Letrozole Dose
≥ 30	No dosage adjustment required.	No dosage adjustment required.
15 to < 30	200 mg daily*; use only if benefit outweighs risk.	
10 to < 15	No data available.	
< 10		No data; consider potential benefit-risk carefully.

*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. Older patients have an increased risk of osteoporosis and fracture with letrozole.

Dosage based on gender and ethnicity

No clinically relevant effects of gender or race on ribociclib pharmacokinetics parameters.

back to top

F - Adverse Effects

Refer to ribociclib , letrozole drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting	• Fatigue • Diarrhea • Alopecia • Constipation	• ↑ cholesterol • Headache, musculoskeletal pain • Estrogen deprivation symptoms • Rash, pruritus (may be severe) • Anorexia, weight loss • ↑ LFTs (may be severe) • Edema • Osteoporosis, fracture • Dyspnea • Insomnia • Mucositis • Abdominal pain	• Venous thromboembolism • Arrhythmia • QT interval prolonged • Cardiotoxicity • Syncope • Abnormal electrolyte(s) • Hypersensitivity • Eye disorders • Pneumonitis

back to top

G - Interactions

Refer to ribociclib , letrozole drug monograph(s) for additional details.

- Avoid concomitant use of ribociclib with strong CYP3A inhibitors due to ↑ risk of ribociclib exposure. If concomitant use is unavoidable, reduce 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).
- Avoid concomitant use of ribociclib with strong CYP3A inducers that may ↓ ribociclib exposure.
- Avoid concomitant use of ribociclib with CYP3A4 substrates with a narrow therapeutic index due to ↑ risk of CYP3A4 substrate exposure. If unavoidable, consider reducing the dose of CYP3A4 substrate.
- Avoid concomitant use of ribociclib with tamoxifen or with drugs known to prolong QT, disrupt electrolyte levels or reduce heart rate due to ↑ risk of arrhythmia.
- Avoid concomitant use of letrozole with tamoxifen, other anti-estrogens, estrogenic or estrogen-containing therapies due to risk of decreased letrozole efficacy.
- Avoid grapefruit, grapefruit juice, or grapefruit-containing products which may increase ribociclib levels.

back to top

H - Drug Administration and Special Precautions

Refer to ribociclib , letrozole drug monograph(s) for additional details.

Administration: Ribociclib

- 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.

Administration: Letrozole

- Tablets should be taken with a glass of water, with or without food
- Letrozole tablets should be taken at around the same time every day with ribociclib tablets.
- Tablets should not be crush or chewed.
- Missed doses should be taken as soon as possible, but should be skipped if within a few hours (e.g. within 2 or 3 hours) of the next planned dose. Do not double the dose due to over-proportionality of exposure at doses above 2.5 mg daily.
- Store tablets at room temperature (15-30°C).

Contraindications

- Patients with hypersensitivity to ribociclib or letrozole, or any components in their formulation, or other aromatase inhibitors
- Ribociclib is contraindicated in 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).
- Letrozole is contraindicated in premenopausal*, pregnant and/or breastfeeding women, and patients under 18 years of age.

**not receiving ovarian suppression*

Warnings/Precautions

- Few men were included in clinical trials of letrezole. Management of breast cancer in men are generally extrapolated from clinical trials in women.
- Letrozole is not indicated in hormone-receptor negative disease.
- 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 ribociclib use in patients with uncorrected hypokalemia, hypomagnesemia, or hypocalcemia.
- Use ribociclib in caution in patients at risk of thromboembolic events.
- Patients should exercise caution when driving or operating machinery as fatigue, dizziness, somnolence or syncope have been reported with ribociclib and/or letrozole.
- Some brands of letrozole contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Pregnancy/Lactation

- This treatment is **contraindicated** 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).
- Breatsfeeding is **contraindicated** during this treatment, and for at least **21 days** after the last dose.
- Fertility effects: Probable

back to top

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

- 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
- Bone mineral density; Baseline and as clinically indicated
- Serum cholesterol and lipids evaluation; Baseline and as clinically indicated
- Clinical toxicity assessment of infection, bleeding, thromboembolism, fatigue, estrogen deprivation symptoms, pneumonitis, eye problems, cardiac, bone, GI, GU, skin and musculoskeletal effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Outpatient prescription for home administration

back to top

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).

Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018;29:1541-1547.

Ribociclib and letrozole drug monographs, Ontario Health (Cancer Care Ontario).

Tripathy D, Im S, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial.

April 2021 Updated rationale, dose modifications, adverse effects, interactions, drug administration and special precautions, and monitoring sections

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not

undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top