Regimen Monograph

A - Regimen Name

LETR Regimen

Letrozole

Disease Site Breast

Intent Adjuvant

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 adjuvant treatment in postmenopausal women with hormone-receptor positive early breast cancer*
- For the extended adjuvant treatment in postmenopausal women with hormone-receptor positive early breast cancer, after 5 years of tamoxifen treatment

*Aromatase inhibitors (AIs) have been used in the neoadjuvant setting in some clinical trials; AIs generally demonstrated higher breast conserving surgery rates with superior or similar response rates to tamoxifen. However, neoadjuvant AI use has not been approved by Health Canada.

Supplementary Public Funding

letrozole

ODB - General Benefit (letrozole) (ODB Formulary)

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B - Drug Regimen

letrozole	2.5 mg	PO	Daily

For extended adjuvant therapy, start within 3 months of completion of approximately 5 years of tamoxifen

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

Upfront treatment: For 5 years
Switch strategy: For 2-3 years (as a switch after 2-3 years of tamoxifen) for a total of 5 years of endocrine therapy
Extended adjuvant therapy: For 3-5 years, after completing 5 years of tamoxifen

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D - Premedication and Supportive Measures

Antiemetic Regimen: Not applicable

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.

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E - Dose Modifications

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

Dosage with toxicity

Dosage in myelosuppression: No dosage adjustment required.

Hepatic Impairment

Hepatic Impairment	Letrozole Dose
Mild to Moderate (Child-Pugh Class A or Class B)	No dose adjustment needed, although exposure may ↑ by 37%.
Severe (Child-Pugh C)	No data. Monitor patients closely and consider dose modification.

Renal Impairment

Creatinine Clearance (mL/min)	Letrozole Dose
≥ 10	No dose adjustment needed.
< 10	No data. Consider potential benefit-risk carefully.

Dosage in the Elderly

No dosage adjustment required. Older patients have an increased risk of osteoporosis and fracture.

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F - Adverse Effects

Refer to 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
• Estrogen deprivation symptoms	• Fatigue • Headache, musculoskeletal pain • Edema	• ↑ Cholesterol • Dizziness • Constipation • Nausea, vomiting • Osteoporosis, fracture	• Arterial thromboembolism • Venous thromboembolism • Arrhythmia • Cardiotoxicity • Cataracts • Hypersensitivity • Rash

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G - Interactions

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

- Avoid concomitant use with tamoxifen, other anti-estrogens, estrogen-containing or estrogenic therapies due to the risk of decreased letrozole efficacy.

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H - Drug Administration and Special Precautions

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

Administration:

- Tablets should be taken with a glass of water, with or without food, at around the same time every day.
- Tablets should not be crushed 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 known hypersensitivity to letrozole, or any of its components, or other aromatase inhibitors.
- Premenopausal women*
- Pregnant and/or breastfeeding women
- Patients under 18 years of age

**not receiving ovarian suppression*

Warning/Precautions:

- Few men were included in clinical trials. Management of breast cancer in men are generally extrapolated from clinical trials in women.
- Letrozole is not indicated in hormone-receptor negative disease.
- Use of letrozole in the adjuvant setting should be carefully considered for patients with osteoporosis or risk factors for cardiovascular events or osteoporosis.
- Carefully assess benefit-risk before using letrozole as extended adjuvant treatment for early breast cancer patients with low recurrence risk, as an increase in deaths was observed in node-negative patients in the letrozole arm as compared to patients on placebo.
- Some brands contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Pregnancy/Lactation:

- Letrozole is **contraindicated** in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least:
  - **20 days** after the last dose for females (product monograph recommendation) or
  - **6 months** after the last dose for males (general recommendation).
- Breastfeeding: **Contraindicated**
- Fertility effects: Probable

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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

- Serum cholesterol and lipids evaluation; Baseline and as clinically indicated
- Bone mineral density; Baseline and as clinically indicated
- LH, FSH and/or estradiol levels (in patients whose menopausal status is unclear or who become amenorrheic after chemotherapy); Baseline and regularly during the first 6 months of treatment
- Clinical toxicity assessment of fatigue, estrogen deprivation symptoms, musculoskeletal, cardiovascular, thromboembolism, GI and GU effects, ophthalmic, dermatologic effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

BIG 1-98 Collaborative Group, Mouridsen H, Giobbie-Hurder A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009;361(8):766-76.

Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001;12(11):1527-32.

Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for erbB-1– and/or erbB-2–positive, estrogen receptor–positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001;19(18):3808-16.

Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. JCO 2008;26(12):1948-55.

Goss P, Ingle J, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. NEJM 2003;349(19):1793-802.

Letrozole drug monograph. Ontario Health (Cancer Care Ontario).

Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up. Lancet Oncol 2011;12(12):1101-8.

PEBC Advice Documents or Guidelines

- Optimal Systemic Therapy for Early Female Breast Cancer

November 2020 Updated adverse effects and monitoring sections; expanded interactions, drug administration and special precautions sections

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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.

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