Drug Monograph

A - Drug Name

letrozole

COMMON TRADE NAME(S): Femara®

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B - Mechanism of Action and Pharmacokinetics

Letrozole is a selective non-steroidal aromatase inhibitor and inhibits the conversion of adrenally generated androstenedione to estrone or estradiol by aromatase in peripheral tissues (e.g., adipose tissue), as well as in tumours. It significantly lowers serum estradiol concentration in postmenopausal women and has no detectable effect on thyroid function, formation of adrenal corticosteroids or aldosterone and plasma androgen levels.

Absorption	Bioavailability	99.9%
	Effects with food	Not significantly affected by food
	Time to reach steady state	2 to 6 weeks
Distribution	Rapidly and extensively distributed into tissues.	
	PPB	60% (albumin)
Metabolism	The major route of elimination is via metabolism (CYP 2A6 and 3A4) to a pharmacologically inactive carbinol metabolite (CGP44645), followed by glucuronidation. Doses above 2.5 mg daily produce over-proportional increases in exposure, possibly due to a saturation of metabolic elimination processes.	

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	Active metabolites	No
	Inactive metabolites	Yes
Elimination	Letrozole and metabolites are excreted mainly via the kidneys.	
	Urine	88% of dose within 2 weeks (mostly as metabolites)
	Feces	4% of dose within 2 weeks
	Half-life	2 to 5 days (terminal)

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C - Indications and Status

Health Canada Approvals:

- For first-line treatment of advanced hormone-receptor positive breast cancer in postmenopausal women
- For hormonal treatment of advanced/metastatic hormone-receptor positive breast cancer after relapse or disease progression, in women with natural or artificially-induced postmenopausal endocrine status, who have previously been treated with anti-estrogens
- For adjuvant treatment of postmenopausal women with hormone-receptor positive invasive early breast cancer*
- For the extended adjuvant treatment of hormone-receptor positive invasive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy*

Notes:

*Marketing approvals are based on disease-free survival as no improvement in overall survival was shown. The risk of death in node-negative patients was increased compared to placebo in the extended adjuvant setting.

Other Uses:

- Ovarian cancer

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D - Adverse Effects

Emetogenic Potential: Not applicable

The following table contains adverse events reported in ≥ 2% of patients in an extended adjuvant treatment study of early breast cancer in postmenopausal women. It also includes severe, life-threatening, or post-marketing adverse events from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (4%)	E
	Arterial thromboembolism (3%)	D
	Cardiotoxicity (rare)	D
	Hypertension (8%)	E
	Venous thromboembolism (1%)	D
Dermatological	Alopecia (6%)	D
	Rash (2%) (may be severe)	E
Gastrointestinal	Abdominal pain (5%)	E
	Anorexia (8%)	E
	Constipation (18%)	I E
	Diarrhea (8%)	I E
	Dyspepsia (5%)	I
	Nausea, vomiting (18%)	I E
	Weight changes (3%)	E
General	Edema (28%)	E
	Fatigue (47%)	E
Hematological	Leukopenia (rare)	E
Hepatobiliary	↑ LFTs (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I
Metabolic / Endocrine	↑ Cholesterol (23%)	D
	Hyperglycemia (3%)	E
Musculoskeletal	Fracture (13%)	D
	Musculoskeletal pain (42%)	E
	Osteoporosis (15%)	D
Nervous System	Anxiety (4%)	E
	Depression (7%)	E

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	Dizziness (22%)	E
	Headache (32%)	E
	Insomnia (9%)	E
	Memory impairment (2%)	E
Ophthalmic	Cataract (<1%)	D
	Eye disorders (Blurred vision, eye irritation; rare)	D
Reproductive and breast disorders	Estrogen deprivation symptoms (up to 61%)	E
	Vaginal dryness (8%)	E
Respiratory	Cough, dyspnea (9%)	E

* "*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 letrozole include estrogen deprivation symptoms, fatigue, musculoskeletal pain, headache, edema, ↑ cholesterol, dizziness, constipation, nausea, vomiting, and osteoporosis.

Letrozole, when used in the metastatic setting, is associated with a lower overall incidence of thromboembolic events as compared to tamoxifen. When compared to megestrol, lower weight gain and vaginal bleeding have been observed with letrozole, but higher incidences of **hot flashes, headache, rash, nausea, musculoskeletal pain, other gastrointestinal effects** and **peripheral edema** were reported with letrozole.

In the adjuvant early breast cancer trial, there were higher rates of **osteoporosis, fractures, hypercholesterolemia, arthralgia, myalgia, MI** and **CHF** when compared to tamoxifen, but reduced incidences of thromboembolic events, uterine polyps, vaginal hemorrhage and endometrial hyperplasia.

In the extended adjuvant study (median treatment duration of 60 months), significantly higher rates of **cardiovascular events** (including arterial or venous thromboembolism) were observed in the letrozole group (9.8%), as compared to placebo (7%; median treatment duration 60 months). A significantly higher incidence of osteoporosis was observed in the patients who received letrozole (14.5%) than those who received placebo (7.8%).

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E - Dosing

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Refer to protocol by which patient is being treated.

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.

Adults:

Oral: 2.5 mg Daily

Dosage with Toxicity:

Dosage in myelosuppression: No dosage adjustment required.

Dosage with 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 Class C)	No data. Monitor patients closely and consider dose modification.

Dosage with Renal Impairment:

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

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Dosage in the elderly:

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

Children:

CONTRAINDICATED in patients under 18 years of age. Safety and efficacy not established.

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F - Administration Guidelines

- 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).

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G - Special Precautions

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*

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Other Warnings/Precautions:

- 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.

Other Drug Properties:

- Carcinogenicity: Unknown
  An increased incidence of benign ovarian stromal tumours was observed in animal studies.

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Spontaneous abortions and congenital anomalies have been reported.
- Teratogenicity: Yes
  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
  Administration of letrozole to female rats resulted in decreased mating/pregnancy ratios and increased pre-implantation loss. Administration of letrozole to male rats resulted in decreased sperm count and motility and testicular changes; severe reductions in the number of sperm-positive and pregnant females were evident.

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H - Interactions

Administration with cimetidine had no significant effect on letrozole's pharmacokinetics, and letrozole had no significant effect on warfarin's pharmacokinetic parameters.

However, letrozole is a **strong inhibitor of CYP2A6** and a **moderate inhibitor of CYP2C19** (at doses higher than those achieved with clinical doses). Caution is advised with concomitant

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administration of drugs with a narrow therapeutic index (e.g. phenytoin, clopidogrel) that are mainly metabolized by these isoenzymes.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Tamoxifen, other anti-estrogens, estrogen-containing or estrogenic agents	May ↓ letrozole efficacy; tamoxifen ↓ letrozole levels by 38% on average	Unknown	Avoid concomitant use
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ letrozole concentration or adverse effects (theoretical)	↓ letrozole metabolism	Caution with strong CYP3A4 inhibitors (theoretical)
CYP2A6 inhibitors (e.g. methoxsalen, tranylcypromine)	↑ letrozole concentration or adverse effects (theoretical)	↓ letrozole metabolism	Caution with strong CYP2A6 inhibitors (theoretical)
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ letrozole concentration or efficacy (theoretical)	↑ letrozole metabolism	Caution with strong CYP3A4 inducers (theoretical)

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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
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

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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 - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- letrozole

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K - References

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists, p. 1104-9.

Product Monograph: Femara® (letrozole). Novartis Pharmaceuticals Canada, July 20, 2017.

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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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