Letrozole: Drug information

(For additional information see "Letrozole: Patient drug information" and see "Letrozole: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Femara

Brand Names: Canada

ACH-Letrozole; Apo-Letrozole; Auro-Letrozole; Bio-Letrozole; Femara; JAMP-Letrozole; Mar-Letrozole; MED-Letrozole; Nat-Letrozole; PMS-Letrozole; RAN-Letrozole; Riva-Letrozole; Sandoz-Letrozole; Teva-Letrozole; Van-Letrozole; Zinda-Letrozole

Pharmacologic Category

Antineoplastic Agent, Aromatase Inhibitor

Dosing: Adult

Breast cancer, advanced (first- or second-line treatment): Females: Postmenopausal: Oral: 2.5 mg once daily; continue until tumor progression

Breast cancer, early (adjuvant treatment): Females: Postmenopausal: Oral: 2.5 mg once daily for a planned duration of 5 years; discontinue at relapse.

Duration of therapy: American Society of Clinical Oncology (ASCO) guidelines for Adjuvant Endocrine Therapy of Hormone Receptor-Positive Breast Cancer (Focused Update) recommend a maximum duration of 5 years of aromatase inhibitor therapy for postmenopausal women; aromatase inhibitors may be combined with tamoxifen for a total duration of up to 10 years of endocrine therapy. Refer to the guidelines for specific recommendations based on menopausal status and tolerability (Burstein 2014). Treatment with an additional 5 years of therapy (for a total of 10 years of aromatase inhibitor therapy) has demonstrated a significantly improved rate of disease-free survival and a decreased risk of disease recurrence and contralateral breast cancer (when compared to placebo), although overall survival was not significantly different between groups and bone-related adverse events occurred more frequently with letrozole versus placebo (Goss 2016).

Breast cancer, early (extended adjuvant treatment): Females: Postmenopausal: Oral: 2.5 mg once daily for a planned duration of 5 years (after 5 years of tamoxifen); discontinue at relapse. In clinical trials, letrozole was initiated within 3 months of discontinuing tamoxifen (Goss 2003; Jin 2012).

Duration of therapy: ASCO guidelines for Adjuvant Endocrine Therapy of Hormone Receptor-Positive Breast Cancer (Focused Update) recommend a maximum duration of 5 years of aromatase inhibitor therapy for postmenopausal women; aromatase inhibitors may be combined with tamoxifen for a total duration of up to 10 years of endocrine therapy. Refer to the guidelines for specific recommendations based on menopausal status and tolerability (Burstein 2014). Treatment with an additional 5 years of therapy (for a total of 10 years of aromatase inhibitor therapy) has demonstrated a significantly improved rate of disease-free survival and a decreased risk of disease

recurrence and contralateral breast cancer (when compared to placebo), although overall survival was not significantly different between groups and bone-related adverse events occurred more frequently with letrozole versus placebo (Goss 2016).

Off-label combinations:

Breast cancer, advanced, estrogen receptor-positive, HER2-negative: Females: Oral: 2.5 mg once daily (in combination with palbociclib) until disease progression or unacceptable toxicity (Finn 2015) **or** 2.5 mg once daily (in combination with ribociclib) until disease progression or unacceptable toxicity (Hortobagyi 2016)

Breast cancer, metastatic, hormone receptor-positive, HER2-positive: Females: Oral: 2.5 mg once daily (in combination with lapatinib) until disease progression or unacceptable toxicity (Johnston 2009)

Infertility/ovulation stimulation in anovulatory women with polycystic ovarian syndrome (PCOS; off-label use): Oral: 2.5 to 7.5 mg daily on cycle days 3 to 7 (Franik 2014; Legro 2013; Legro 2014; Misso 2012). Up to 5 treatment cycles may be administered with the dose increased in subsequent cycles for nonresponse or poor ovulatory response as determined by progesterone levels; maximum dose 7.5 mg daily (Legro 2014). Additional trials may be necessary to further define the routine use of letrozole in infertile women with PCOS.

Ovarian (epithelial) cancer (off-label use): Oral: 2.5 mg once daily; continue until disease progression (Ramirez 2008)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl ≥10 mL/minute: No dosage adjustment necessary.

CrCl <10 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Hepatic Impairment

Mild to moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary.

Severe impairment (Child-Pugh class C) and cirrhosis: 2.5 mg every other day

Noncirrhotic patients with elevated bilirubin: There are no dosage adjustments provided in the manufacturer's labeling (effect has not been determined).

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Femara: 2.5 mg

Generic: 2.5 mg

Generic Equivalent Available (US)

Yes

Administration Administer orally with or without food.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

Use **Breast cancer in postmenopausal women:** Adjuvant treatment of hormone receptor-positive early breast cancer, extended adjuvant treatment of early breast cancer after 5 years of tamoxifen; treatment of advanced breast cancer with disease progression following antiestrogen therapy; first-line treatment of hormone receptor-positive or hormone receptor-unknown, locally-advanced, or metastatic breast cancer

Use: Off-Label

Infertility/ovulation stimulation in anovulatory women with polycystic ovarian syndrome (PCOS); Ovarian (epithelial) cancer, recurrent

Medication Safety Issues

Sound-alike/look-alike issues:

Femara may be confused with Famvir, femhrt, Provera

Letrozole may be confused with anastrozole

International issues:

Letaris, a formerly marketed Dutch brand name product for letrozole, may be confused with Letairis, a US brand name for ambrisentan.

Adverse Reactions

>10%:

Cardiovascular: Edema (7% to 18%)

Central nervous system: Headache (4% to 20%), dizziness (3% to 14%), fatigue (8% to 13%)

Dermatologic: Diaphoresis (≤24%), night sweats (15%)

Endocrine & metabolic: Hypercholesterolemia (3% to 52%), hot flash (6% to 50%), weight gain (2% to 13%)

Gastrointestinal: Nausea (9% to 17%), constipation (2% to 11%)

Neuromuscular & skeletal: Weakness (4% to 34%), arthralgia (8% to 25%), arthritis (7% to 25%), ostealgia (5% to 22%), back pain (5% to 18%), decreased bone mineral density (≤5% to 15%),

osteoporosis (≤5% to 15%), bone fracture (10% to 14%)

Respiratory: Dyspnea (6% to 18%), cough (6% to 13%)

1% to 10%:

Cardiovascular: Chest pain (6% to 8%), hypertension (5% to 8%), chest wall pain (6%), peripheral edema (5%), cerebrovascular accident (2% to 3%; including hemorrhagic stroke, thrombotic stroke), thromboembolism (2% to 3%; including portal vein thrombosis, pulmonary embolism, thrombophlebitis, venous thrombosis), angina pectoris (1% to 2%), myocardial infarction (1% to 2%), transient ischemic attacks

Central nervous system: Insomnia (6% to 7%), pain (5%), anxiety (<5%), depression (<5%), vertigo (<5%), drowsiness (3%)

Dermatologic: Skin rash (5%), alopecia (3% to 5%), pruritus (1%)

Endocrine & metabolic: Weight loss (6% to 7%), hypercalcemia (<5%)

Gastrointestinal: Diarrhea (5% to 8%), vomiting (3% to 7%), abdominal pain (6%), anorexia (1% to 5%), dyspepsia (3%)

Genitourinary: Mastalgia (2% to 7%), urinary tract infection (6%), vaginal dryness (5%), vaginal hemorrhage (5%), vaginal irritation (5%)

Hematologic & oncologic: Metastases (2% to 4%)

Infection: Infection (7%), influenza (6%), viral infection (6%)

Neuromuscular & skeletal: Limb pain (4% to 10%), myalgia (7% to 9%)

Ophthalmic: Cataract (2%)

Renal: Renal disease (5%)

Respiratory: Pleural effusion (<5%)

<1%, postmarketing, and/or case reports: Anaphylaxis, angioedema, arterial thrombosis, blurred vision, cardiac failure, carpal tunnel syndrome, dysesthesia, dysgeusia, endometrial carcinoma, endometrial hyperplasia, erythema multiforme, eye irritation, fever, hepatitis, hypoesthesia, increased appetite, increased liver enzymes, increased thirst, irritability, leukopenia, memory impairment, nervousness, palpitations, paresthesia, stomatitis, tachycardia, tenosynovitis (trigger finger), thrombocytopenia, toxic epidermal necrolysis, urinary frequency, urticaria, vaginal discharge, xeroderma, xerostomia

Contraindications

Use in women who are or may become pregnant

Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to letrozole, other aromatase inhibitors, or any component of the formulation; use in patients <18 years of age; premenopausal endocrine status; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

• CNS depression: May cause dizziness, fatigue, and somnolence; patients should be cautioned before performing tasks which require mental alertness (eg, operating machinery or driving).

• Decreased bone mineral density: May cause decreases in bone mineral density (BMD). A decrease in hip BMD by 3.8% from baseline in letrozole-treated patients vs 2% in placebo at 2 years has been demonstrated; however, there was no statistical difference in changes to the lumbar spine BMD scores. Monitor BMD.

• Increased cholesterol: May increase total serum cholesterol. In patients treated with adjuvant therapy and cholesterol levels within normal limits, an increase of ≥1.5 x ULN in total cholesterol has been demonstrated in 8.2% of letrozole-treated patients (25% requiring lipid-lowering medications) vs 3.2% of tamoxifen-treated patients (16% requiring medications). Monitor cholesterol panel; may require antihyperlipidemics.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; dose adjustment recommended in patients with cirrhosis or severe hepatic dysfunction.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Other warnings/precautions:

• Appropriate use: Not generally indicated for known hormone-receptor negative disease.

Metabolism/Transport Effects

Substrate of CYP2A6 (minor), CYP3A4 (minor); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP2A6 (strong)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Artesunate: CYP2A6 Inhibitors may decrease serum concentrations of the active metabolite(s) of Artesunate. CYP2A6 Inhibitors may increase the serum concentration of Artesunate. *Risk X: Avoid combination*

CYP2A6 Substrates: CYP2A6 Inhibitors (Strong) may decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

Methadone: Aromatase Inhibitors may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Tamoxifen: May decrease the serum concentration of Letrozole. *Risk C: Monitor therapy*

Tegafur: CYP2A6 Inhibitors (Strong) may decrease serum concentrations of the active metabolite(s) of Tegafur. Specifically, CYP2A6 inhibitors may inhibit the conversion of tegafur into its active metabolite, 5-

fluorouracil. *Risk X: Avoid combination*

Pregnancy Risk Factor

X (show table)

Pregnancy Implications

Adverse events were observed in animal reproduction studies. Letrozole is approved for use in postmenopausal women only (no clinical benefit for breast cancer has been demonstrated in premenopausal women). Use in women who are or who may become pregnant is contraindicated. Women who are perimenopausal or recently postmenopausal should use adequate contraception until postmenopausal status is fully established.

Breast-Feeding Considerations

It is not known if letrozole is present in breast milk. Due to the potential for serious adverse reactions in the breastfeeding infant, a decision should be made to discontinue breastfeeding or the drug, taking into account the importance of treatment to the mother.

Dietary Considerations

Calcium and vitamin D supplementation are recommended.

Monitoring Parameters

Monitor periodically during therapy: Complete blood counts, thyroid function tests; serum electrolytes, cholesterol, transaminases, and creatinine; blood pressure; bone density

For infertility/ovarian stimulation (off-label use), a pregnancy test is recommended prior to initiation. Midluteal progestin concentrations (in a clinical study, nonresponse to treatment was defined as a progesterone concentration <3 ng/mL during the midluteal phase; poor ovulatory response was defined as progesterone concentrations indicating ovulation but just above the cutoff point) (Legro 2014).

Mechanism of Action

Nonsteroidal competitive inhibitor of the aromatase enzyme system which binds to the heme group of aromatase, a cytochrome P450 enzyme which catalyzes conversion of androgens to estrogens (specifically, androstenedione to estrone and testosterone to estradiol). This leads to inhibition of the enzyme and a significant reduction in plasma estrogen (estrone, estradiol and estrone sulfate) levels. Does not affect synthesis of adrenal or thyroid hormones, aldosterone, or androgens.

Pharmacodynamics/Kinetics

Absorption: Rapid and well absorbed; not affected by food

Distribution: V_d: ~1.9 L/kg

Protein binding, plasma: Weak

Metabolism: Hepatic via CYP3A4 and 2A6 to an inactive carbinol metabolite

Half-life elimination: Terminal: ~2 days

Time to steady state, plasma: 2 to 6 weeks; steady state serum concentrations are 1.5 to 2 times higher than single-dose values. In girls 3 to 9 years, steady state concentrations were 25% to 67% that of the mean adult values (Feuillan 2007)

Excretion: Urine (90%; 6% as unchanged drug, 75% as glucuronide carbinol metabolite, 9% as unidentified metabolites)

Pricing: US

Tablets (Femara Oral)

2.5 mg (30): $842.50

Tablets (Letrozole Oral)

2.5 mg (30): $543.44

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Antif (PE); Aromara (ID); Avomit (HR); Bretra (KR); Elozora (RO); Endofree (BD); Esmara (KR); Etruzyl (UA); Famara (UA); Femaplex (ID); Femar (IS, NO); Femara (AE, AR, AT, AU, BD, BE, BG, BH, BO, BR, CH, CL, CN, CO, CY, CZ, DE, DK, EE, EG, ES, FI, FR, GB, GR, HK, HR, HU, IE, IL, IQ, IR, IT, JO, JP, KR, KW, LB, LK, LT, LU, LV, LY, MT, MX, MY, NL, NO, NZ, OM, PE, PH, PK, PL, PR, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, SY, TH, TR, TW, UY, VE, VN, YE); Femgard (CO); Femolet (AU); Fera (AU); Fezol (BD); Fu Rui (CN); Gesamef (CR, DO, GT, HN, NI, PA, SV); Hentrozole (PH); Lenara (KR); Lenor (BD); Lentronat (SG); Letara (AU, NZ); Letero (SG, TH); Letoripe (PH); Letov (LK, TH); Letraz (ID); Letrol (BD); Letrostad (PH); Letroz (PH, PY); Letzol (IN); Lexel (BD); Lezol (PH); Lezra (ID, PH, SG, UA, VN); Likarda (LV); Losiral (EC); Oncolet (LK); Trodis (CR, DO, GT, HN, NI, PA, SV); Trozet (PH, TH, TW); Zolet (LK); Zolstro (CR, DO, GT, HN, NI, PA, SV)

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