DRUG NAME: Letrozole

SYNONYM(S): Letzazole, CGS 20267

COMMON TRADE NAME(S): FEMARA® (notice of compliance,[1] May 1997; patent expires[2] April 2010)

CLASSIFICATION: Aromatase inhibitor

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Letrozole is a reversible (Type II), nonsteroidal aromatase inhibitor. Aromatase catalyzes the final and rate-limiting step in the conversion of androgens to estrogens in peripheral tissues. This occurs mainly in adipose tissue, but also in normal and malignant breast tissues, and provides the main source of estrogen in postmenopausal women. The goal of hormone therapy in breast cancer is to deprive tumour cells of estrogens, which are implicated in the development or progression of tumours.[3,4] Maximal estrogen suppression is produced by a 0.1 mg dose,[3,5] although a higher dose (ie, 2.5 mg per day) was associated with increased clinical responses.[3] Maximal estrogen suppression occurs 48-78 hours after a single dose.[6] Highly selective blockade of aromatase does not interfere with the production of other steroids (eg, adrenal corticosteroids, aldosterone)[7,8] or thyroid stimulating hormone.[5] Letrozole does not have progestogenic, androgenic or estrogenic activity.[7,8] Differences in the mechanism of action may contribute to the apparent lack of cross-resistance between steroidal (eg, exemestane) and nonsteroidal (eg, anastrozole, letrozole) aromatase inhibitors.[9]

PHARMACOKINETICS:

Interpatient variability	no information found	
Oral Absorption	rapidly and completely absorbed[10]; food decreases absorption.[11]	
	time to peak plasma concentration	1 h under fasting condition and 2 h after eating[11]
Distribution	rapid, extensive distribution into tissues.[10]Steady-state level 7 times higher than the level after a single dose and achieved after 2-6 weeks.	
	cross blood brain barrier?	no information found
	volume of distribution	1.9 ± 0.5 L/kg [10]
	plasma protein binding	60%
Metabolism	metabolized by hepatic cytochrome P450 (3A4 and 2A6)	
	active metabolite(s)	none
	inactive metabolite(s)	CGP 44645
Excretion	mainly renal excretion	
	urine	6% as unchanged; 84% as metabolites[12]
	terminal half life	48 h
	clearance[10]	2.21 ± 0.65 L/h
Gender	no information found	
Elderly	no clinically significant difference[13]	
Children	no information found	
Ethnicity	no information found	

Adapted from reference[6] unless specified otherwise.

USES:

Primary uses:
∗Breast cancer[14-16]

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Carcinogenicity: Letrozole caused benign ovarian stromal tumours and hepatocellular adenoma and carcinoma in animal studies.[13]

Mutagenicity: Not mutagenic in Ames test. Letrozole is clastogenic in mammalian *in vitro* but not *in vivo* chromosome tests.[6,13]

Fertility: Letrozole caused sexual inactivity and atrophy of the reproductive tract in animal studies.[13]

Pregnancy: FDA Pregnancy Category D.[13] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[6]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[17]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiovascular (general)	cardiovascular events (4%)[18]
	peripheral edema (9-17%)[18]
	phlebitis/thromboembolism (0.6%)
constitutional symptoms	fatigue (11-30%)[18]
	sweating (1-22%)[18]
	weight gain (6%)
dermatology/skin	hair thinning (3%)
	rash (6%)
endocrine	***hot flashes*** (6-47%)[18]
gastrointestinal	*emetogenic potential*: non-emetogenic[14,15]
	anorexia (5%)
	constipation (8-10%)[18]
	diarrhea (6%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dyspepsia (5%)
	increased appetite (1%)
	nausea (11%)
	vomiting (8%)
hemorrhage	vaginal bleeding (2-4%)[18]
hepatic	elevated gamma-glutamyltransferase (4%)
metabolic/laboratory	***hypercholesterolemia*** (4-12%)[15,18]
musculoskeletal	arthritis (6%)[18]
	fracture (4%)[18]
	osteoporosis (6%)[18]
neurology	dizziness (3-12%)[18]
	insomnia (3%)
	somnolence (3%) [15]
pain	abdominal pain (6%)
	arthralgia/myalgia (12-21%)[18]
	chest pain (7%)
	headache (13-18%)[18]
	musculoskeletal pain (arms, legs, back) (27%)
pulmonary	cough (8%)
	dyspnea (9%)
sexual/reproductive function	vaginal bleeding (see under "hemorrhage")
	vaginal discharge (2%)

Adapted from reference[14] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
estrogen (estrogen replacement therapy, Premarin, C.E.S., Estracomb, Estraderm)	may interfere with therapeutic effect of letrozole	estrogen can counter the estrogen suppression effect of letrozole	see below

AGENT	EFFECT	MECHANISM	MANAGEMENT
tamoxifen	tamoxifen decreases plasma letrozole level by 38%, but has no significant effect on estrogen suppression by letrozole[19]; letrozole has no effects on the pharmacokinetics of tamoxifen and its major metabolites[20]	possibly increased letrozole metabolism by inducing cytochrome P450 3A4	avoid concurrent therapy outside clinical trials

Estrogen use with letrozole: use other options for conditions in which estrogen is indicated. If estrogen is used, prescribe the lowest dose to relieve symptoms, monitor patient carefully and consider short term use.[21] For vaginal complaints such as dyspareunia, dryness and sexual dysfunction, topical estrogen may be considered. Estring produces a local effect with systemic levels measurable only for the first 24 hours of the three month ring. Premarin cream can be used but may have variable systemic levels related to the absorption through the vaginal tissues. The lowest dose to relieve symptoms should be used.[22]

SUPPLY AND STORAGE:

Oral:
Novartis Pharmaceuticals Canada Inc., Sandoz Canada Inc., Accord Healthcare Inc., and Cobalt Pharmaceuticals Inc. supply letrozole as 2.5 mg tablets. Tablets contain lactose. Store at room temperature.[23-26]

Pharmascience Inc. supplies letrozole as 2.5 mg tablets. Tablets contain lactose and tartrazine. Store at room temperature.[27]

Teva Canada Limited and Generic Medical Partners supply letrozole as 2.5 mg tablets. Tablets contain tartrazine. Store at room temperature.[28,29]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BCCA usual dose noted in ***bold, italics***

Oral:	***2.5 mg PO once daily.*** Administer with food or on empty stomach.[6]
Dosage in renal failure:	No adjustment required with CrCl > 10 mL/min. Dosing information not available with CrCl < 10 mL/min.[6]
Dosage in hepatic failure:	No adjustment required with mild to moderate hepatic dysfunction. Dosing information not available with severe hepatic dysfunction.[6]
Dosage in dialysis:	no information found

REFERENCES:

1. Health Canada Therapeutic Products Programme. Notices of compliance (NOC)-Drugs. Available at: http://www.hc-sc.gc.ca/hpb-dgps/therapeutic/htmleng/noc-drugs.html. Accessed 15 September, 2000.
2. Health Canada Therapeutic Products Programme. Patent register. Available at: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/patents.html. Accessed 15 September, 2000.

3. Njar VC, Brodie AM. Comprehensive pharmacology and clinical efficacy of aromatase inhibitors. Drugs 1999;58(2):233-55.
4. Santen RJ, Harvey HA. Use of aromatase inhibitors in breast carcinoma. Endocrine-Related Cancer 1999;6(1):75-92.
5. Lipton A, Demers LM, Harvey HA, et al. Letrozole (CGS 20267). A phase I study of a new potent oral aromatase inhibitor of breast cancer. Cancer 1995;75(8):2132-8.
6. Novartis Pharmaceuticals Canada Inc. Femara product monograph. 5 September 2000.
7. Bajetta E, Zilembo N, Dowsett M, et al. Double-blind, randomised, multicentre endocrine trial comparing two letrozole doses, in postmenopausal breast cancer patients. European Journal of Cancer 1999;35(2):208-13.
8. Iveson TJ, Smith IE, Ahern J, et al. Phase I study of the oral nonsteroidal aromatase inhibitor CGS 20267 in postmenopausal patients with advanced breast cancer. Cancer Research 1993;53(2):266-70.
9. Kvinnsland S, Anker G, Dirix LY, et al. High activity and tolerability demonstrated for exemestane in postmenopausal women with metastatic breast cancer who had previously failed on tamoxifen treatment. European Journal of Cancer 2000;36(8):976-82.
10. Sioufi A, Gauducheau N, V P, et al. Absolute bioavailability of letrozole in healthy postmenopausal women. Biopharmaceutics and Drug Disposition 1997;18(9):779-89.
11. Sioufi A, Sandrenan N, Godbillon J, et al. Comparative bioavailability of letrozole under fed and fasting conditions in 12 healthy subjects after a 2.5 mg single oral administration. Biopharmaceutics and Drug Disposition 1997;18(6):489-97.
12. Lamb HM, Adkins JC. Letrozole. A review of its use in postmenopausal women with advanced breast cancer. Drugs 1998;56(6):1125-40.
13. Letrozole. USP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2000.
14. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. Journal of Clinical Oncology 1998;16(2):453-61.
15. Gershanovich M, Chaudri HA, Campos D, et al. Letrozole, a new oral aromatase inhibitor: randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Letrozole International Trial Group (AR/BC3). Annals of Oncology 1998;9(6):639-45.
16. Ingle JN, Johnson PA, V S, et al. A randomized phase II trial of two dosage levels of letrozole as third-line hormonal therapy for women with metastatic breast carcinoma. Cancer 1997;80(2):218-24.
17. Susan Ellard MD. Personal Communication. BC Cancer Agency Breast Tumour Group; 14 January 2005.
18. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349(19):1793-802.
19. Dowsett M, Pfister C, Johnston SR, et al. Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. Clinical Cancer Research 1999;5(9):2338-43.
20. Ingle JN, V S, Johnson PA, et al. Evaluation of tamoxifen plus letrozole with assessment of pharmacokinetic interaction in postmenopausal women with metastatic breast cancer. Clinical Cancer Research 1999;5(7):1642-9.
21. BC Cancer Agency Breast Tumour Group. Hormone replacement therapy after a diagnosis of breast cancer. Vancouver, BC Cancer Agency 2000;5 May 2000.
22. Brian Norris MD. Personel Communication. BC Cancer Agency Breast Tumour Group; 15 March 2001.
23. Novartis Pharmaceuticals Canada Inc. FEMARA® product monograph. Dorval, Quebec; 29 September 2008.
24. Sandoz Canada Inc. SANDOZ LETROZOLE® product monograph. Boucherville, Quebec; 6 April 2010.
25. Accord Healthcare Inc. LETROZOLE® product monograph. Markham, Ontario; 26 February 2010.
26. Cobalt Pharmaceuticals Inc. LETROZOLE® product monograph. Mississauga, Ontario; 25 January 2010.
27. Pharmascience Inc. pms-LETROZOLE® product monograph. Montreal, Quebec; 27 April 2009.
28. Teva Canada Limited. LETROZOLE® product monograph. Toronto, Ontario; 10 February 2010.
29. Generic Medical Partners. MED-LETROZOLE® product monograph. Toronto, Ontario; 22 February 2010.