A DRUG NAME: LETROZOLE

COMMON TRADE NAME(S): **Femara® (Novartis)**

B MECHANISM OF ACTION AND PHARMACOKINETICS

Aromatase (estrogen synthetase) is an enzyme that catalyses various steps in the conversion of androgen to estrogen. Letrozole is a potent and selective non-steroidal aromatase inhibitor. Letrozole inhibits the conversion of adrenally generated androstenedione to estrone or estradiol by aromatase in peripheral tissues, such as adipose tissue, as well as in tumours. It inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme. It significantly lowers serum estradiol concentration in postmenopausal women and has no detectable effect on formation of adrenal corticosteroids or aldosterone. In estrogen-dependent tumours, estrogen deprivation causes growth arrest and possibly, tumour cell death.

Oral Absorption	Letrozole is rapidly and completely absorbed from the gastrointestinal tract (absolute bioavailability is 99.9%). The extent of absorption is not significantly affected by food; therefore, letrozole may be taken with or without food.	
Distribution	Letrozole is rapidly and extensively distributed into tissues.	
	Cross blood brain barrier?	Unknown
	PPB	60% (albumin)
Metabolism	The major route of elimination of letrozole is via metabolism to a pharmacologically inactive carbinol metabolite. Both cytochrome P450 isoenzymes 2A6 and 3A4 are involved in the biotransformation. Letrozole and its metabolites are excreted mainly via the kidneys.	
	Active metabolite(s)	No
	Inactive metabolite(s)	Yes (CGP 44645)
Excretion	Letrozole and its metabolites are excreted mainly via the kidneys.	
	Urine	88% (6% unchanged)
	Terminal $T_{1/2}$	2 days

C INDICATIONS AND STATUS

***** For first line hormonal treatment of advanced breast cancer in postmenopausal women.

* For hormonal treatment of advanced breast cancer in postmenopausal women, who have disease progression following anti-estrogen therapy.

* For the extended adjuvant treatment of hormone receptor-positive early breast cancer in postmenopausal women who have received approximately 5 years of prior standard adjuvant tamoxifen therapy.

**** Health Canada approved indication***

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT	ONSET
Cardiovascular	Thromboembolism/CVA (2%)	D
	Palpitations (rare)	E
	Peripheral edema (6%)	E
Central nervous system	Dizziness (1%)	E
	Parasthesiae	E
	Depression, anxiety	E
	Insomnia/somnolence	E
	Headache (7%)	E
Dermatologic	Rash, pruritus (3%)	E
	Alopecia (6%)	D
Endocrine	Hot Flushes (17%)	D
Gastrointestinal	Nausea (7%) Vomiting (3%)	I
	Eye irritation	E
	Increased appetite (1-2%)	E
	Constipation (2%), abdominal pain	E
	Anorexia (2%)	I
	Dyspepsia (3%)	I
Genitourinary	Vaginal bleeding and discharges (2%), UTI	E
General	Fatigue (5%), fever	E
	Tumour, breast pain	E
	Leukopenia	
	Dyspnea (1%), dry mouth	
	Weight gain or loss (2%)	D
Hepatic	Increased LFTs	
	Hypercholesterolemia (3%)	D

D ADVERSE EFFECTS (Continued)

ORGAN SITE	SIDE EFFECT	ONSET
Musculoskeletal	Osteoporosis	
	Pain (2%), myalgia, arthralgia	E

Dose-limiting side effects are underlined.
I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

The majority of the adverse events seemed to be mild to moderate in severity, and many are expected effects on estrogen withdrawal. The most commonly reported events associated with letrozole included **nausea, headache, fatigue, hot flushes** and **peripheral edema**.

Letrozole was also associated with a lower overall incidence of cardiovascular events (including thromboembolic events) and weight gain when compared to megestrol, but a higher incidence of rash, nausea and other gastrointestinal effects and peripheral edema.

Patients treated with aromatase inhibitors may be at a higher risk for cardiovascular events as well as osteoporosis. Patients should be carefully monitored and treated appropriately.

E DOSING

Refer to protocol by which patient is being treated.

Adult:

The recommended dose is 2.5mg once daily.

Dosage in Elderly: No dosage adjustment required.

Dosage in Myelosuppression: No dosage adjustment required.

Dosage in Renal Failure: No dosage adjustment is required in patients with creatinine clearance ≥10mL/min. No data are available for patients with creatinine clearance <10mL/min. The potential risks and benefits to such patients should be considered carefully before prescribing letrozole.

Dosage in Hepatic Failure: No dosage adjustment is required in patients with mild to moderate hepatic failure. Patients with severe hepatic impairment should be kept under closer supervision for adverse events as they are exposed to a significantly higher level of letrozole and dose modification may be considered.

Children: Safety and efficacy not established.

F ADMINISTRATION GUIDELINES (see Appendix 3a)

- Oral self-administration; drug available by retail prescription.

G SPECIAL PRECAUTIONS

Letrozole is **contraindicated** in patients with known hypersensitivity to letrozole, or any of its components, or other aromatase inhibitors. It is also contraindicated in women with **premenopausal endocrine status**, in **pregnancy,** and /or **lactation**. Letrozole is ***teratogenic*** and ***fetotoxic*** and causes fetal malformations. The ***mutagenic and carcinogenic*** potential of letrozole is not known.

H INTERACTIONS

Administration with cimetidine had no effect on letrozole's pharmacokinetics, and letrozole had no 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). Even though CYP2A6 does not play a major role in drug metabolism, the potential for some drug interactions may exist; thus, caution is advised with concomitant administration of drugs, whose disposition is mainly dependent on these isoenzymes, especially if the therapeutic index is narrow.

Coadministration with tamoxifen leads to a significant decrease in letrozole levels. The clinical significance of this is not clear.

I RECOMMENDED CLINICAL MONITORING

Recommended Clinical Monitoring	**Suggested Clinical Monitoring**
NO RECOMMENDED TOXICITY RATINGS	NO ADDITIONAL TOXICITY RATINGS

J REFERENCES

Compendium of Pharmaceuticals and Specialties. 2006. Femara®. Canadian Pharmacists Association.

Lamb HM , Adkins JC. Letrozole: a review of its use in postmenopausal women with advanced breast cancer. Drugs 1998 Dec;56(6): 1125-40.

Levien T, Baker DE. Letrozole and Budesonide Inhalation powder.
Hospital Pharmacy 1997; 33(4):437-54.

McEvoy G (ed): American formulary drug information service 2001. American society of Health-System Pharmacists, Bethesda: 1035-6.

Mouridsen H, Gershanovich M, Sun Y et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of international letrozole breast cancer group. J Clin Oncol 2001; May 15: 19(10): 2596-606.

Worthington I (ed): Current drug topics (newsletter): letrozole. Metrodis, Toronto, October 1996: 15: 125.