Letrozole Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.	C50	371a	CDS
Extended adjuvant treatment of hormone-dependent-invasive breast cancer in postmenopausal women who have received prior adjuvant endocrine therapy for 5 years	C50	371b	CDS
Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status.	C50	371c	CDS
Neo-adjuvant treatment of postmenopausal women with hormone receptor positive breast cancer.	C50	371d	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Letrozole is administered orally once daily continuously during treatment.

Duration of adjuvant treatment and treatment of advanced breast cancer will be determined by the prescribing Consultant and depends on disease progression or unacceptable toxicity.

In the neoadjuvant setting, treatment with letrozole could be continued for 4 to 8 months in order to establish optimal tumour reduction. If the response is not adequate, treatment with letrozole should be discontinued and surgery scheduled and/or further treatment options discussed with the patient.

Drug	Dose	Route	Diluent & Rate	Cycle
Letrozole	2.5mg daily	PO	NA	Continuous daily as indicated until disease progression or unacceptable toxicity
Daily oral supplement of calcium and Vit D are recommended for duration of therapy.				
Tablet should be swallowed whole. Can be taken with food or on an empty stomach with a glass of water				
A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose (within 2 or 3 hours), the missed dose should be skipped, and the patient should go back to her regular dosage schedule. Doses should not be doubled because with daily doses over the 2.5 mg recommended dose, over-proportionality in systemic exposure was observed				

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to letrozole or any of the excipients
- Hormone receptor-negative
- Premenopausal endocrine status

- Pregnancy and breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or General Practitioner under direction of plan written by medical oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Check FSH, LH, oestradiol levels if less than 55 and prior hysterectomy or uncertain menopausal status due to young age or other factors.
- Consider baseline bone density assessment in appropriate patients.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- No recommended dose modifications.
- Any dose modification should be discussed with a Consultant.

Renal Impairment	Hepatic Impairment
No dose adjustment necessary in patients with CrCl ≥10ml/min	No dose adjustment is required for patients with mild to moderate hepatic insufficiency (Child-Pugh A or B). Insufficient data are available for patients with severe hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) require close supervision

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy).**

PREMEDICATIONS:

None usually required

OTHER SUPPORTIVE CARE:

Daily oral supplements of calcium and vitamin D are recommended for the duration of the therapy. Lifestyle modification including regular exercise, particularly weight bearing exercises should be encouraged.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatic dysfunction:** Aromatase inhibitors are considered safe in mild-to- moderate hepatic dysfunction but have not been studied in severe hepatic dysfunction.
- **Bone density:** Letrozole is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement of adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered depending on the patient's safety profile
- **Hyperlipidemia:** An increase in cholesterol or triglyceride levels may occur when an aromatase inhibitor is initiated. Consideration should be given to checking levels during the first few months of therapy, especially in those patients with prior significant lipid elevations.
- **Tendonitis and tendon rupture:** Tendonitis and tendon rupture (rare) may occur. Close monitoring of the patient and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon

DRUG INTERACTIONS:

- Co-administration of letrozole with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole.
- Oestrogen preparations (e.g. topical vaginal creams etc.) should be avoided as these may negate the effect of aromatase inhibitors.
- Metabolism of letrozole is partly mediated via CYP2A6 and CYP3A4. Cimetidine, a weak, unspecific inhibitor of CYP450 enzymes, did not affect the plasma concentrations of letrozole. The effect of potent CYP450 inhibitors is unknown.
- In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g.phenytoin).
- Current drug interaction databases should be consulted for more information

ATC CODE:

Letrozole	L02BG04

REFERENCES:

1. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005;353(26):2747-2757.
2. Mouridsen H, GiobbieHurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009;361(8):766-776.
3. Eisen A, Trudeau M, Shelley W, et al. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review. Cancer Treat Rev 2008;34(2):157-174.

4. 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 the International Letrozole Breast Cancer Group. J Clin Oncol 2001;19(10):2596-2606.
5. Ellis M J, 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;19:3808-16.
6. Femara® Summary of Product Characteristics Accessed Nov 2020 Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0896-012-001_25112019114744.pdf

Version	Date	Amendment	Approved By
1	11/11/2018		Prof Maccon Keane
2	26/11/2018	Updated to new NCCP template. Updated dosing in severe hepatic impairment Clarification on duration of treatment	Prof Maccon Keane
3	9/12/2020	Reviewed. Updated exclusion criteria and adverse events section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.