Scottish Medicines Consortium

letrozole 2.5mg tablets (Femara®) No. 152/05

Novartis Pharmaceuticals (UK) Ltd

4 February 2005 *(updated September 2005)*

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Letrozole (Femara®) is accepted for restricted use within NHS Scotland for the treatment of invasive early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy. Treatment should continue for 3 years or until tumour relapse, whichever occurs first.

Following 5 years of adjuvant tamoxifen therapy the risk of recurrence (in ipsilateral breast, new tumour in contralateral breast or distance metastases) occurs at an aggregate rate of 2-3% per year. The use of letrozole as extended adjuvant treatment resulted in a 43% lower risk of recurrence compared with placebo. However, a significant difference for overall survival, defined as time to death from any cause, was seen in lymph-node positive patients only. Clinicians and patients should consider the residual risk of recurrence, individual preferences and the risks and benefits of treatment.

Letrozole is restricted to initiation to breast cancer specialists.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Letrozole 2.5mg tablets (Femara®)

Licensed indication under review

Treatment of invasive early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.

Dosing information under review

Letrozole 2.5mg once daily, orally. Treatment should continue for 3 years or until tumour relapse, whichever occurs first.

UK launch date

October 2004

Comparator medications

None

Cost per treatment period and relevant comparators

Drug	Dose	Annual Cost (£)
Letrozole	**2.5 mg once daily**	**£1084**

Summary of evidence on comparative efficacy

There is one clinical trial supporting the use of letrozole for this new indication. Results from the interim analysis were reported to the independent Data and Safety Monitoring Committee in August 2003, and the study was unblinded on 9 October 2003. The results of interim analyses were published in November 2003 and since then, further analyses have taken place on data up until the unblinding of the study. These data are unpublished and have been supplied by Novartis Pharmaceuticals, in the form of a clinical overview some of which are commercial in confidence and therefore have not been included.

One randomised double blind placebo controlled trial recruited 5187 women with a histologically confirmed primary breast cancer, = 50 years at start of tamoxifen treatment or <50 years at start of tamoxifen treatment and either postmenopausal, or had a bilateral oophorectomy, or premenopausal and amenorrhoeic during chemotherapy or treatment with tamoxifen, or had postmenopausal levels of luteinizing hormone or follicle stimulating hormone. Women were eligible if they were disease-free after completing 5 years (=4.5 and <6 years) of adjuvant tamoxifen treatment within the previous 3 months, had a tumour that was positive for oestrogen, progesterone or both, and had a Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (scored on a scale of 0 to 5, with lower scores indicating better function). Exclusion criteria included concurrent use of investigational drugs, and history of, or the presence of another type of cancer other than skin cancer or carcinoma in situ of cervix. In addition, concomitant systemic hormone replacement therapy or concomitant treatment with a selective oestrogen receptor modulator was contraindicated although intermittent treatment with vaginal oestrogens was allowed.

A sample size of 4800 was calculated with an 80% power and based on a four-year disease free survival rate of 88% in the placebo group and a difference of 2.5%. Two interim analyses

were planned after 171 events and 342 events had occurred. Early termination of the trial could be considered at the time of the interim analysis, based on a log rank test with the use of the Lan deMets alpha spending function with O'Brien-Fleming boundaries. The intention to treat population comprised 2575 and 2582 in the letrozole and placebo groups, respectively. The interim analysis gave results from a median of 2.4 years of follow-up. For the extended analyses reported in the clinical overview, the median follow-up was 27.5 months and median duration of treatment was 24 months.

Two sub-studies assessing the effect a) on spine and hip bone mineral densities and b) assessing the effect on serum lipids were carried out on 226 and 347 patients, respectively.

Primary endpoints

The primary end-point of disease-free survival was defined as time from randomisation to recurrence of the primary disease (in breast, chest wall, or nodal or metastatic sites), or the development of a new primary breast cancer in the contralateral breast. In the final analysis, the number of events in the letrozole and placebo groups were 92 and 155 respectively, which gave a hazard ratio of 0.58 95% CI (0.45, 0.76), p= 0.00003 and resulted in a 42% lower risk of recurrence with letrozole than with placebo. In the published results, the number of events in the letrozole and placebo groups were 75 and 132 respectively, giving a hazard ratio of 0.57 95% CI (0.43, 0.75) representing a 43% lower risk, p=0.00008.

Secondary endpoints, sub-group analysis and uncontrolled trials

There was no significant difference for the secondary end-point of overall survival, defined as time to death from any cause. The number of patients who died in the letrozole and placebo groups were 51 and 62, respectively which gave a hazard ratio of 0.82 95% CI (0.56, 1.19), p=0.291. In the published analysis, the hazard ratio for death from any cause comparing letrozole and placebo was 0.76 95% CI (0.48, 1.21), p=0.25. Exploratory analysis of overall survival when stratification factors were considered showed a statistically significant difference for lymph node positive patients only. The numbers of deaths in the letrozole and placebo groups were 28 and 45, respectively, (p=0.035).

Summary of evidence on comparative safety

The safety population comprises 5136 patients who had taken = 1 dose of study drug. Adverse events, assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0), were collected by using a checklist of adverse effects associated with aromatase inhibitors (e.g. hot flushes, sweating, evidence of osteoporosis, vaginal bleeding) as well as spontaneous reporting. Adverse events reported in the clinical overview occurred with a frequency of >10% in any treatment group and with a reporting frequency of at least 1% difference between treatment arms. Flushing, arthralgia/arthritis, and myalgia were more common in the letrozole group (p<0.001) and vaginal bleeding was more common in the placebo group (p<0.001).

Adverse events that occurred with a frequency of >10% in any treatment group and with a reporting frequency of at least 1% difference between treatment arms were reported in the published paper. Flushing, arthralgia, arthritis, and myalgia were significantly more common in the letrozole group and vaginal bleeding was more common in the placebo group.

There was a significant difference in the number of patients reporting new osteoporosis (letrozole, 6.9% versus placebo, 5.5%; p=0.042), however the fracture rate was similar for both groups. The bone sub-study found a significant difference in the change from baseline in hip bone mineral density (letrozole, 3% versus placebo, 0.4%; p=0.048) at 24 months. There were no differences between the groups in lipid levels.

Summary of clinical effectiveness issues

The clinical study recruited women who discontinued tamoxifen therapy less than 3 months before commencing letrozole. Therefore the efficacy of letrozole has not been assessed in women who have discontinued tamoxifen therapy more than 3 months prior to letrozole treatment being considered.

The optimal duration of treatment has not been defined in the clinical trial due to the early discontinuation of the study. Therefore, following standard adjuvant tamoxifen treatment, the use of letrozole for 5 years cannot be recommended. The summary of product characteristics for letrozole includes a statement that treatment with letrozole should continue for 3 years or until tumour relapse occurs, whichever comes first.

More patients in the letrozole group compared with the placebo group reported new onset osteoporosis. Due to early discontinuation of the trials the long-term effects of letrozole on bone resorption may have been underestimated. The summary of product characteristics recommends bone mineral density assessment and initiating treatment or prophylaxis for osteoporosis in women with osteoporosis or at risk of osteoporosis. The addition of bisphosphonates to aromatase inhibitors is currently being investigated in a clinical trial setting.

The long-term effects of letrozole on serum lipid levels, beyond a median treatment duration of 24 months, have not been evaluated.

Summary of comparative health economic evidence

A Markov cohort model examining the costs and health outcomes of 1000 62-year-old women treated with letrozole for five years (or three years) versus no active treatment post tamoxifen was provided. The model followed the patients over a total time span of 38 years through a variety of possible Markov states; disease free, dead, contralateral breast cancer, loco-regional recurrence or metastatic event (soft tissue, bone or visceral). Transition probabilities were derived from the short-term trial data for the initial four years of the model and for the subsequent year using regression techniques. For all subsequent years in the model it was assumed that both disease-free letrozole treated patients and disease-free no treatment patients would have the same probabilities of experiencing any event. Literature values were utilised to derive transition probabilities from other health states in the model. Deterministic and probabilistic sensitivity analyses were provided.

Assuming five years of letrozole treatment, the result showed an incremental cost per QALY of £15,640 for all patients, £12,240 if only node-positive women were treated or £21000 if only node-negative women were treated. If letrozole therapy were to be used for three years only, the incremental cost per QALY overall was £14,000. The cost effectiveness ratios doubled if the lower 95% confidence interval for event rates was used. Probabilistic sensitivity analysis indicated that there was an 80% chance that letrozole was cost-effective at a threshold of £30000 per QALY for node-negative patients and a 95% chance for node-positive patients. The model did not take into account any possible long-term effects on osteoporosis (or its treatment) or lipid levels.

The comparator for the evaluation was appropriate as currently women cease tamoxifen treatment at five years (unless they are part of a clinical trial). The model provided a useful structure over which to examine likely long-term outcomes by extrapolating results from the

clinical trial. The model did not however account for the impact that any serious side effects such as osteoporosis could have on costs and outcomes. The sensitivity analyses were useful in showing that the results were reasonably robust but importantly that the assumed rate of disease free survival was key in driving the result.

Budget impact

The estimated annual budget impact of using letrozole is £120,000 in year 1 rising to £1.2M by year 5. These calculations assume that there would be a steady incident population of 738 women per year, that letrozole would be given for three years and that uptake of treatment would range from 30% in the first year to 76% by year five.

Guidelines and protocols

A Scottish Intercollegiate Guidelines Network (SIGN) guideline on *The Treatment of Breast cancer* is due in Spring 2005.

The National Institute for Clinical Excellence (NICE) produced an updated edition of *Improving Outcomes in Breast Cancer in 2002*. There is no guidance on the treatment of early breast cancer after 5 years of tamoxifen treatment as the guideline predates the results of the letrozole study. The remit of a new NICE guideline on *Breast Cancer: diagnosis and treatment,* which includes the use of hormonal treatments, has been agreed. The date of issue of this guideline has not been confirmed.

The American Society of Clinical Oncology (ASCO) Technology Assessment on *the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer* was updated in November 2004. The panel concluded that an aromatase inhibitor should be used as adjuvant hormonal therapy for intitial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 11 January 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

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