Scottish Medicines Consortium

letrozole, 2.5mg tablets (Femara®) No. 251/06

Novartis Pharmaceuticals UK Ltd

7 April 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises the NHS Boards and Area Drug and Therapeutic Committees (ADTCs) 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 adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

Letrozole has shown benefit over standard anti-oestrogen therapy in terms of disease-free survival, although a pre-planned sub-group analysis showed a statistically significant beneficial effect in node-positive patients but not node-negative patients. It offers an alternative to existing treatment and has a different range of adverse effects.

Another aromatase inhibitor is available for the same indication at a lower cost.

Treatment with letrozole should be initiated by a breast cancer specialist.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Letrozole 2.5mg tablet (Femara®)

Indication

Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer. Treatment should continue for 5 years or until tumour relapse occurs, whichever comes first.

Dosing information

2.5mg once daily

UK launch date

1 December 2005

Comparator medications

Comparator medicines for adjuvant hormone therapy in early breast cancer are tamoxifen and anastrozole. In addition the combination regimen, tamoxifen for 2 or 3 years followed by exemestane for 3 or 2 years is also licensed.

Cost of relevant comparators

Drug	Dose	Annual cost (£)*	5-year cost (£)*
Letrozole	**2.5mg daily for 5 years**	**1084**	**5420**
Tamoxifen	20mg daily for 5 years	34	170
Tamoxifen ? exemestane	Tamoxifen 20mg for 2/3 years then exemestane 25mg for 3/2 years	Not applicable	2161-3309
Anastrozole	1mg daily for 5 years	894	4470

* Costs from eVadis drug dictionary accessed on 1 February 2006.

Summary of evidence on comparative efficacy

Letrozole is a non-steroidal aromatase inhibitor that blocks production of oestrogen. Following surgery for operable breast cancer the standard hormone therapy has been tamoxifen given for five years. However, recent advances have resulted in regimens which include an aromatase inhibitor (given either sequentially after two, three or five years of tamoxifen or in place of tamoxifen for five years) gaining approval from the Scottish Medicines Consortium.

One randomised, controlled, phase III, double-blind trial recruited 8010 post-menopausal women with breast cancer positive for oestrogen receptors, progesterone receptors or both. The trial had four arms; letrozole 2.5mg daily for 5 years, tamoxifen 20mg daily for 5 years, letrozole for 2 years followed by tamoxifen for 3 years and tamoxifen for 2 years followed by

letrozole for 3 years. The primary analysis compared the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially. Events and follow-up in the sequential treatment groups were included up to 30 days after treatments were switched. Further data from the sequentially treated patients are not yet available. The primary end-point was disease-free survival, defined as time from randomisation to recurrence at local, regional or distant sites, a new invasive cancer in the contra-lateral breast, any second non-breast cancer or death without a prior cancer event. Secondary end-points included overall survival (time from randomisation to death from any cause) and systemic disease-free survival (time from randomisation to systemic recurrence, excluding local and contra-lateral breast events).

The median follow-up was 25.8 months and the percentage of patients completing 5 years treatment was approximately 16%. For the primary end-point of disease-free survival the number of events in the letrozole and tamoxifen groups were 351 and 428 respectively. Disease-free survival was significantly greater in the letrozole compared with the tamoxifen group (hazard ratio (HR): 0.81, 95% confidence interval (CI) 0.70-0.93, p=0.003). The five-year estimates of disease-free survival were 84.0% and 81.4% for the letrozole and tamoxifen groups respectively. Planned sub-group analysis showed a significant beneficial effect of letrozole for node-positive patients; HR: 0.71, 95% CI 0.59-0.85, p<0.001 but not for node-negative patients; HR: 0.96, 95% CI 0.76-1.21, p=0.75. The hazard ratios for systemic disease-free survival (0.83; 95%CI 0.72-0.97) and overall survival (0.86; 95%CI 0.70-1.06) favoured letrozole although the results were significant for systemic disease-free survival only (p=0.02).

Summary of evidence on comparative safety

The incidence of fractures (5.7% for letrozole vs 4.0% for tamoxifen), cardiac failure (0.8% vs 0.4%) and arthralgia (20.3% vs 12.3%) were significantly more common in the letrozole group than in the tamoxifen group. The Summary of Product Characteristics states that during adjuvant treatment with letrozole, women with osteoporosis or risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry (e.g. DEXA scanning) at the commencement of treatment. The percent of patients in whom hypercholesterolaemia was observed at least once during treatment was 44% (grade 1, 35%) and 19% (grade 1, 17%) in the letrozole and tamoxifen groups respectively. However, the median change in cholesterol value at 24 months was -1.8% and -14.1% for the letrozole and tamoxifen groups respectively. Lipid levels were assessed from non-fasting blood samples which make the results more difficult to interpret.

In contrast, adverse events significantly more common in the tamoxifen group than in the letrozole group included thromboembolic events (1.5% for letrozole vs 3.5% for tamoxifen), vaginal bleeding (3.3% vs 6.6%) and hot flushes (34% vs 38%). The tamoxifen group also required more endometrial biopsies (9.1% vs 2.3%).

Summary of clinical effectiveness issues

In the intention to treat population, disease-free survival showed a significantly greater effect for letrozole compared with tamoxifen. However, sub-group analysis showed this was significant for node-positive patients only. An editorial published at the same time as the study stated that longer term follow-up is important, in order to define the benefit of letrozole in patients with node-negative disease.

Two specific adverse effects warrant further investigation. The risk of bone fracture increases as bone mineral density (BMD) decreases. Therefore, more information on the long term

effects on BMD is required to determine if longer term letrozole therapy poses a greater fracture risk than that reported in the clinical trial. Furthermore, it is noted that new approaches to reduce the fracture risk are being studied in the clinical trial setting. Secondly, the increased incidence of grade 3-5 cardiac events with letrozole compared with the tamoxifen group may in part be due to the protective effect of tamoxifen on the arteries. However the adverse effect requires further study.

There are no randomised controlled trials directly comparing the efficacy and safety of aromatase inhibitors in women with early breast cancer in the adjuvant setting.

Summary of comparative health economic evidence

A cost utility analysis submitted by the manufacturer reported a base cost per QALY gained of £12,000 for letrozole versus tamoxifen in the 5 year treatment of postmenopausal women with early breast cancer after surgery. The primary data source for clinical effectiveness was the clinical trial of letrozole versus tamoxifen. A Markov model was developed to extrapolate the health benefits (life-years-gained and QALYs) and costs associated with lower recurrence and distant metastases rates with letrozole for a cohort of women aged 61 years old over a lifetime horizon (set as 39 years to age 100).

The economic model used was comprehensive and took into account the health impact and costs associated with treatment related adverse events (which favour tamoxifen in the analysis). In addition, a conservative assumption regarding the duration of treatment benefit of 5 years was used, after which no difference in event recurrence rates for letrozole and tamoxifen patients was assumed. The main limitation of the analysis was the multitude of data sources and modelling assumptions used for event rates and the costs estimates and uncertainty concerning the utility data used. However, results from sensitivity analyses indicate that letrozole can be considered a cost-effective alternative to tamoxifen for the adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer. A cost-effectiveness analysis against the other aromatase inhibitor anastrozole, licensed for the same indication, was not performed.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The budget impact is estimated to be £171,000 in year 1 for the treatment of an estimated 154 patients, rising to an annual cost of £1.6 million by year 5 for the treatment of 1,621 women. There are potential health care cost savings from reduced recurrence rates estimated to be £200,000 by year 5 but only very limited cost offsets from reduced tamoxifen use. However, the net budget impact will be less due to the current use of anastrozole.

Guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) issued guideline number 84, management of breast cancer in women, in December 2005. Tamoxifen is considered first line choice as initial therapy in the adjuvant setting, with an aromatase inhibitor being considered if there are relative contraindications or intolerance to tamoxifen. In addition the

guideline recommends that postmenopausal patients should be considered for a switch to an aromatase inhibitor after either two to three years, or after five years of tamoxifen therapy.

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 published in 2004. It states that an aromatase inhibitor is the treatment of choice as initial adjuvant therapy for any postmenopausal women with hormone receptor positive invasive breast cancer with a contraindication to tamoxifen. For women who do not have a contraindication to tamoxifen, it remains unclear if initial treatment with an aromatase inhibitor is superior, equivalent or inferior to a planned cross-over from tamoxifen to an aromatase inhibitor after a fixed point in time. The panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Woman with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.

The National Institute of Health and Clinical Excellence (NICE) have agreed a final protocol on hormonal therapies for the adjuvant treatment of early oestrogen receptor positive breast cancer and plan to report in November 2006.

Additional information

The Scottish Medicines Consortium (SMC) accepted anastrozole for restricted use within NHS Scotland in August 2005, for the adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer. In addition, anastrozole was previously accepted for restricted use within NHS Scotland in March 2004, for the adjunctive treatment of early breast cancer in postmenopausal women with oestrogen-receptor positive disease who cannot take tamoxifen because of the presence of thrombophilic disorders or a past history of venous thromboembolic events, endometrial malignancy or undiagnosed vaginal bleeding.

The SMC accepted exemestane for restricted use within NHS Scotland in October 2005, for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy.

The SMC accepted letrozole for restricted use within NHS Scotland in February 2005, for the treatment of invasive early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.

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 April 2006.

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

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Winer E.P, Hudis C, Burstein H.J et al. American Society of Clinical Oncology. Technology Assessment on the use of Aromatase Inhibitors as Adjuvant Therapy for Postmenopausal Women with Hormone Receptor Positive Breast Cancer; Status Report 2004. Journ of Clin Oncol; 23(3):1-11.

Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. New England Journal of Medicine. 2005: 353; 2747-2757.

Swain S. Aromatase inhibitors – a triumph of translational oncology (editorial) New England Journal of Medicine. 2005: 353; 2807-2809