Scottish Medicines Consortium

exemestane 25mg tablets (Aromasin®) No. (210/05)
Pfizer Limited

New indication for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy.

4 October 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises 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

Exemestane (Aromasin®) is accepted for restricted use within NHS Scotland for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy.

Exemestane has shown benefit in terms of disease-free survival when given as an alternative to tamoxifen after initial adjuvant treatment with tamoxifen for 2-3 years. It offers an alternative to tamoxifen after initial adjuvant treatment with tamoxifen for 2-3 years and has a different adverse effects profile. Treatment with exemestane is restricted to initiation by a breast cancer specialist.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

exemestane 25mg daily (Aromasin®)

Indication

The adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy.

Dosing information

25mg daily

UK launch date

15 September 2005

Comparator medications

Tamoxifen, anastrozole, letrozole.

Cost of relevant comparators

Drug	Dose	Annual costs	Two-three year costs
Exemestane	**25mg daily**	£1080	£2160-3240
Anastrozole	1mg daily	£894	£1788-2682
Tamoxifen (generic)	20mg daily	£24	£48-72
Tamoxifen (Nolvadex-D)	20mg daily	£106	£212-318
Letrozole	2.5mg daily	£1084	£2168-3252

Costs were taken from the eVadis database accessed July 2005.

Summary of evidence on comparative efficacy

In postmenopausal women, oestrogens are primarily produced by the conversion of androgens to oestrogens by the aromatase enzyme in peripheral tissues. In breast cancer, oestrogen deprivation through inhibition of the aromatase enzyme offers a selective treatment for hormone dependent breast cancer in postmenopausal women. Exemestane is an irreversible, steroidal aromatase inhibitor with no oestrogenic activity.

The application for the licence extension is supported by one large international, randomised, double-blind trial in 4740 postmenopausal women with oestrogen receptor positive or unknown status and operable unilateral breast cancer who remained disease free after two to three years' adjuvant treatment with tamoxifen. Only an interim analysis with a median follow up of 30.6 months has been published; unpublished results with a median follow up of 34.5 months were submitted for this assessment. To enter the study patients had to have been treated with tamoxifen for 2-3 years and be disease free following treatment for primary disease. Eligible patients were randomised to tamoxifen 20mg daily (n=2372) or exemestane 25mg daily (n=2352), to continue therapy until they had completed 5 years of adjuvant treatment. The primary outcome was disease-free survival, defined as the time from randomisation to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause. Secondary outcomes included overall survival, time to contralateral breast cancer, breast cancer-free survival, distant recurrence-free survival

and long-term tolerability. In selected centres, substudies including quality of life assessments, endometrial status and bone metabolism assessments were undertaken.

At the time of this second interim analysis, 1256 patients (26.6%) were still on therapy, 628 in each group; a total of 968 (20.5%) had been prematurely withdrawn (483 in the exemestane group and 485 in the tamoxifen group) and 2440 patients had completed therapy, 1215 in the exemestane group and 1225 in the tamoxifen group. Median duration of therapy was 27.3 months, median follow up 34.5 months, with 519 first events reported (213 in the exemestane group and 306 in the tamoxifen group). The Kaplan-Meier estimates of disease-free survival at 3 years were 90% in the exemestane group and 86% in the tamoxifen group. The unadjusted hazard ratio of 0.69 (95% CI: 0.58-0.82) for disease-free survival favoured exemestane, representing a 31% relative reduction in the risk of relapse in the observed period. Adjusting for pre-specified prognostic factors did not affect the hazard ratio, 0.66 (95% CI: 0.55, 0.79), and was similar to that estimated from the unadjusted analysis. Women with >3 positive nodes had a higher risk of relapse, hazard ratio 4.50 (95% CI: 3.53-5.72). The secondary outcomes of contralateral breast cancer (8 events versus 25 events, a reduction of 68%) and distant recurrence (133 events versus 187 events, a reduction of 30%) were significantly reduced in the exemestane group. Overall survival was not significantly different between the two groups (116 versus 137 deaths in the exemestane and tamoxifen groups, respectively, p=0.229), with Kaplan-Meier estimates of overall survival at 3 years of 95% (95% CI: 94%, 96%) in the exemestane group and 94% (95% CI: 93%, 95%) in the tamoxifen group, unadjusted hazard ratio 0.86 (95% CI: 0.67, 1.10), representing a 14% relative reduction in the risk of death. Longer follow-up is awaited for more mature survival data. Preliminary results of the impact of exemestane on quality of life published in abstract would suggest no difference compared with tamoxifen, but more complete results are awaited.

Summary of evidence on comparative safety

The incidence of treatment-emergent adverse events was similar for both groups, with most adverse events classed as grade 1-2. The most common adverse events were hot flushes, fatigue and arthralgia. A similar number of patients discontinued in each group with a similar number withdrawing due to adverse events, although more patients withdrew due to recurrence in the tamoxifen group. Serious adverse events were reported by 15% of the exemestane group and 17% of the tamoxifen group. These were judged to be treatment-related for 2.5% of exemestane patients and 3.6% of tamoxifen patients. The most common serious adverse events in the exemestane group were within the nervous system (1.9%), neoplasm (1.8%) and cardiac (1.7%) categories and in the tamoxifen group, within neoplasm (3.3%), reproductive system and breast disorders (2.3%) and nervous system (1.8%) categories. More tamoxifen than exemestane patients experienced neoplasms, and reproductive system and breast disorders.

During the study 54.6% of exemestane and 51.5% of tamoxifen patients had treatment-emergent illnesses. The most commonly reported were cardiovascular disorder (by 12.8% and 10.6% of exemestane and tamoxifen patients, respectively), osteoarthritis (by 5.3% and 4.0% of exemestane and tamoxifen patients, respectively) and osteoporosis (by 4.6% and 2.8% of exemestane and tamoxifen patients, respectively). An analysis of combined illnesses and adverse events showed that compared with tamoxifen, exemestane was associated with a greater incidence of arthralgia, insomnia, pain in limb, osteoporosis, diarrhoea, paraesthesia, carpal tunnel syndrome, epistaxis, neuropathy, osteochondrosis and trigger finger. Tamoxifen was associated with a greater incidence of muscle cramp, thromboembolism, endometrial hyperplasia and uterine polyps.

Preliminary, interim results of the substudies into endometrial status and bone assessment have been published in abstract. These would seem to indicate that exemestane reduces the endometrial abnormalities associated with tamoxifen but it also reduces bone mineral density in the lumbar spine and total hip compared with tamoxifen. Full results are awaited.

Summary of clinical effectiveness issues

Tamoxifen is an oestrogen receptor antagonist with some partial agonist oestrogen-like activity which may protect against bone loss, but may also be associated with an increased risk of thromboembolism and of endometrial abnormalities including malignancy. Exemestane has no oestrogenic activity and therefore does not affect the endometrium adversely. However, the profound reduction in oestrogen concentrations in the circulation have an adverse effect on bone metabolism increasing the rate of bone resorption. The full effect of exemestane on bone metabolism is still being established. Initial treatment with tamoxifen may be beneficial in conserving bone loss before therapy with an aromatase inhibitor. Additional adjuvant therapy with an aromatase inhibitor after treatment with tamoxifen giving a total of 5 years of adjuvant therapy offers the advantage of a reduction in the risk of endometrial abnormalities but the benefit of therapy.

Longer term outcomes are required to show if the advantages of disease-free survival and reduction in recurrence will translate into improvement in overall survival.

There are a number of therapeutic options now available and further studies are required to show if there is any difference in the aromatase inhibitors available and the optimum way to use or combine aromatase inhibitors and tamoxifen to achieve the best results.

Summary of comparative health economic evidence

The submission states that switching to exemestane following 2-3 years' treatment with tamoxifen is cost-effective compared with 5 years' treatment with tamoxifen. Exemestane provides improvements in quality adjusted life years (QALYs) at £14,980 per QALY.

The choice of patient population, comparator and economic modelling approach all seem appropriate. The model time horizon (10 years) is quite short and the cycle length (6 months) is quite long but this is unlikely to seriously bias the results.

The clinical data used were taken from the main randomised controlled trial, and while some of the assumptions about adverse event rates and costs could be challenged, sensitivity analysis shows these are very unlikely to have biased the results.

Resource use and costing was carried out in a transparent and acceptable way. Where the assumptions used could be challenged it was clear from sensitivity analysis that these aspects had little bearing on the final results.

The data were analysed to an acceptable standard. The deterministic sensitivity analysis was quite limited but the results are presented in a transparent way so the likely impact of changes in assumptions could be estimated. In summary, the economic case has been demonstrated.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimates a medicines budget impact to be £94k in year 1 and £1,447k in year 5. Including 'savings' on treating advanced disease, the overall NHS impact is £87k in year 1 and £1,347k in year 5. This is based on eligible patient numbers of 1,733 in year 1 and 4,953 in year 5, with an assumed market share of 5% in year 1 and 27% in year 5.

Guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) publication number 29: Breast Cancer in Women, October 1998, is at present under review.

The National Institute of Health and Clinical Excellence (NICE) is conducting a technology appraisal of hormonal therapies for the adjuvant treatment of early breast cancer, but this is not expected to be published until November 2006. It is also developing a guideline on the diagnosis and treatment of breast cancer, but the expected publication date for this is not yet confirmed.

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.

Additional information

In February 2004 the Scottish Medicines Consortium (SMC) accepted anastrozole for restricted use in adjuvant 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. In August 2005 SMC accepted anastrozole for restricted use in a new indication for adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer as an alternative to tamoxifen as it has a different adverse effects profile. Treatment with anastrozole should be initiated by an oncologist.

In February 2005 the SMC accepted letrozole for use in invasive early breast cancer in postmenopausal women following standard 5-year tamoxifen treatment. Treatment should be continued for 3 years or until tumour relapse whichever occurs first.

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 15 September 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration. The references shaded grey are additional to those supplied with the submission.

References

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