Scottish Medicines Consortium

anastrozole 1mg tablet (Arimidex®) (No. 322/06)

AstraZeneca UK Limited

6 October 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,

anastrozole (Arimidex®) is accepted for restricted use within NHS Scotland for the adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen**.**

In a combined analysis of two trials, switching to anastrozole after 2 years of tamoxifen therapy rather than continuing with tamoxifen resulted in a 3.1% increase in event-free survival at three years follow-up. 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 anastrozole is restricted to initiation by a breast cancer specialist.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

Dosing information

1mg to be taken orally once a day.

UK launch date

July 2006

Comparator medications

Tamoxifen, letrozole, anastrozole and exemestane are licensed for the adjuvant treatment of early breast cancer; anastrozole and exemestane may be used as a switch following 2-3 years of tamoxifen, letrozole may be used following 5 years of tamoxifen, and anastrozole and letrozole may be used as an alternative to tamoxifen. The Scottish Intercollegiate Guidelines Network (SIGN), in the *Management of Breast Cancer in Women* guideline (number 84), recommend tamoxifen as the drug of choice and an aromatase inhibitor if there are relative contraindications or intolerance to its use. The guideline also states that postmenopausal women should be considered for a switch to an aromatase inhibitor after 2 to 3 years, or after 5 years of tamoxifen therapy.

Cost of relevant comparators

Product	Regimen	Annual cost (£)*	Two to three year cost (£)*
Anastrozole	**1mg once daily**	**894**	**1788-2681**
Letrozole	2.5mg once daily	1084	2168-3252
Exemestane	25 mg once daily	1080	2161-3241
Tamoxifen (non-proprietary)	20mg once daily	36	71-107

*costs based on eVadis drug dictionary accessed on 1/8/06.

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.

Summary of evidence on comparative efficacy

The aromatase inhibitors are a group of drugs that cause marked reductions in the levels of circulating oestrogens in postmenopausal women. Anastrozole is a non-steroidal, reversible aromatase inhibitor.

A prospectively-planned, event-driven combined analysis of two randomised, multi-centre, open-label, controlled trials has been published comparing five years of tamoxifen with two years of tamoxifen followed by three years of anastrozole. The trials recruited postmenopausal women of = 80 years or = 75 years with histologically verified, locally radically treated, invasive or minimally invasive oestrogen and/or progesterone-receptor positive breast cancer. Tumour infiltration of no more than ten lymph nodes and absence of organ metastases were also required. Eligible patients had been treated with surgery, +/- radiotherapy and two years of tamoxifen (20mg daily in the first study and 20 or 30mg daily in

the second study). Patients were randomised to anastrozole 1mg daily or to continue with tamoxifen for three years. In the first study patients were randomised at the beginning of tamoxifen therapy with age, tumour stage, nodal status and participating centres as stratification factors and in the second study randomisation was done within two years of tamoxifen treatment with participating centre only considered during randomisation. The time-point of two years post-surgery was used as the starting point for the combined analysis. Baseline characteristics were well balanced between both groups at the starting point for the combined analysis.

The primary endpoint for the prospectively defined combined analysis was event-free survival (EFS), where an event was defined as time to relapse at any site or incidence of contralateral breast cancer. In the combined intention-to-treat (ITT) analyses 3224 patients were included; 1606 in the continuing tamoxifen group and 1618 in the group switched to anastrozole. At a median follow-up of 28 months the hazard ratio for EFS was 0.60, (95% confidence interval [CI] 0.44-0.81, p=0.0009). The percentage of patients surviving event-free at three years from the start of the combined analysis, as estimated by Kaplan Meier analysis, was 92.7% in the tamoxifen group and 95.8% in the anastrozole group, an absolute benefit of 3.1% in favour of anastrozole. The superiority of switching to anastrozole over continuing with tamoxifen was consistent across the sub-groups assessed. There was also a numerical increase in overall survival at three years for patients switched to anastrozole (97%) compared to patients remaining on tamoxifen (96%), although this difference was not statistically significant (p=0.16).

A third randomised, multi-centre trial has been conducted and included postmenopausal node-positive women who had already received primary surgery +/- radiotherapy, +/- chemotherapy and had received two to three years of tamoxifen. Patients were randomised to continue with tamoxifen (20mg daily), or to be switched to anastrozole (1mg daily), to give a total of five years' endocrine treatment. Prior to randomisation, women were stratified according to prior chemotherapy and participating centre. The primary endpoint was disease recurrence (including both locoregional and distant recurrences except contralateral breast cancer). EFS was estimated using the following events; locoregional recurrence, distant metastases, secondary primary tumours (including contralateral breast cancer) and breast cancer-unrelated death. A total of 448 patients were enrolled into the trial (225 and 223 in the tamoxifen and anastrozole groups, respectively) and all patients were included in the ITT analysis. At a median follow-up from randomisation of 36 months the HR for tumour recurrence was 0.35 (95% CI 0.18-0.68, p=0.001) and for EFS was 0.35 (96% CI 0.20-0.63, p=0.0002). The respective hazard ratios at 52 months follow-up were 0.43 (95% CI 0.25-0.73, p=0.001) and 0.42 (95% CI 0.26-0.66, p=0.0001).

A meta-analysis utilizing individual patient data involved 4006 patients; 2009 and 1997 in the anastrozole and tamoxifen groups respectively. At a median follow-up of 30 months the hazard ratios for disease free survival was 0.59 (95% CI 0.48-0.74, p<0.0001) and for overall survival was 0.71(95% CI 0.52-0.98, p=0.038), in favour of anastrozole.

Summary of evidence on comparative safety

In the combined analysis of the two trials there were significantly more reports of fractures (34 vs. 16; Odds Ratio [OR] 2.14, 95% CI 1.14-4.17, p=0.015), and significantly fewer thromboses (3 vs. 12; OR 0.25, 95% CI 0.04-0.92, p=0.034) in patients treated with anastrozole compared with those treated with tamoxifen. There was a trend towards fewer emboli (2 vs. 9, p=0.064) and endometrial cancers (1 vs. 7, p=0.069) in the anastrozole group.

For one of the two trials a number of adverse events were predefined, and were similar between the two groups, with the exception of nausea (25 vs. 10; OR 2.53, 95% CI 1.17-5.92, p=0.0162) and bone pain (213 vs. 177; OR 1.25, 95% CI 1.00-1.56, p=0.0546) which were more prevalent in the anastrozole group.

Summary of clinical effectiveness issues

There are a number of therapeutic options now available and further studies are required to show if there is any differences between the aromatase inhibitors available and the optimum way to use or combine aromatase inhibitors and tamoxifen to achieve best results. Two trials (Breast International Group [BIG1-98] and Tamoxifen Exemestane Adjuvant Multinational [TEAM]) are investigating continuous aromatase inhibitor versus aromatase inhibitor after tamoxifen and are due to report in 2008 at the earliest. Furthermore, results of one extended adjuvant trial where an aromatase inhibitor was given after 5 years of tamoxifen have been published. In addition, there are no randomised controlled trials comparing different aromatase inhibitors in the adjuvant setting.

Overall survival was shown to be significantly improved in the group switched to anastrozole, in the meta-analysis only. Longer term follow-up in the individual trials is required to confirm whether benefits in EFS translate into significantly longer overall survival.

The three trials had key differences between the trial populations, including nodal involvement, grading, prior chemotherapy and type of surgery. The trials have therefore shown superior efficacy for anastrozole in a wide patient group.

The beneficial effect of anastrozole described previously should be placed into context with the hazard ratio for recurrence of 0.59 (in favour of treatment with 5 years of tamoxifen over placebo) which has been estimated by the Early Breast Cancer Trialists' Collaborative Group. Anastrozole improves on tamoxifen, which in turn is superior to placebo.

Summary of comparative health economic evidence

A cost utility analysis was submitted comparing anastrozole with tamoxifen alone in adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen. A Markov model was used and the main data source was the combined analysis which reported that, in patients who had received 2 years of tamoxifen, switching to anastrozole resulted in a 40% reduction in the relative risk of disease recurrence. The model estimates a cost per QALY of £7950 compared to treatment with tamoxifen alone

The main issue in terms of the design of the economic evaluation was the choice of comparator. Clinical expert replies have indicated that exemestane is the current treatment option for this indication, which suggests that treatment with tamoxifen alone is not the appropriate comparator. The manufacturer has subsequently provided an additional analysis comparing anastrozole and exemestane.

The clinical evidence and health benefits were handled appropriately. The utility values used were higher than in some previously published studies but this may reduce the benefits of avoiding advanced disease and hence the analysis is slanted against anastrozole in this respect. Resource use and costs were handled appropriately.

The cost per QALY when anastrozole was compared to tamoxifen is relatively low and an additional indirect comparison provided by the manufacturer suggests that anastrozole is likely to have an acceptable profile of costs and benefits compared to exemestane.

Patient and public involvement

Patient Interest Group Submission: Breast Cancer Care

Budget impact

The manufacturer estimated a net budget impact of £103k in year 2007 and £93k in year 2009. The fall in net budget impact is because the majority of patients diagnosed in years 2001 to 2005 will have finished their adjuvant therapy.

It is estimated that 174 patients will be eligible in 2006 and 228 patients will be eligible in 2009. The manufacturer states that patients who have been on tamoxifen for 1, 4 or 5 years will not be eligible to switch to an aromatase inhibitor as the license is only for patients who have already been on tamoxifen for 2 or 3 years. Also, patients diagnosed in 2006 and beyond are newly diagnosed patients who will be eligible for primary adjuvant treatment with an aromatase inhibitor. The budget impact in comparison to exemestane has not been undertaken.

Guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a guideline on the *Management of Breast Cancer in Women* guideline (number 84) in December 2005.

The National Institute for Health and Clinical Excellence (NICE) is undertaking a Health Technology Appraisal of *hormonal treatments for the adjuvant treatment of early oestrogen receptor-positive breast cancer*. The use of anastrozole as a planned switch is out with the remit of the appraisal as it was not licensed for this indication, at the specified time. Therefore the guidance, in terms of anastrozole, is for primary adjuvant therapy only. The draft guidance is as follows: The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women. The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.

Additional information

The Scottish Medicines Consortium (SMC) has previously reviewed anastrozole and issued the following guidance, following a full submission, in August 2005. Anastrozole (Arimidex) is accepted for restricted use within NHS Scotland in the adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer. Anastrozole has shown benefit over standard anti-oestrogen therapy in terms of disease-free survival in this patient group. It offers an alternative to tamoxifen and has a different adverse effects profile. Treatment with anastrozole should be initiated by a breast cancer specialist. This supersedes the advice issued on February 2004.

The SMC has reviewed exemestane and issued the following guidance, following a full submission, in October 2005. 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.

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 03 November 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.

Jakesz R, Jonat W, Gnant M, et al. Benefits of switching postmenopausal women with endocrine responsive early breast cancer to anastrozole after two years' adjuvant tamoxifen: combined results from 3224 women enrolled in ABCSG trial 8 and the ARNO 95 trial. Lancet 2005;366:455-462

Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial. J Clin Oncol 2005;23(22):5138-47

Boccardo F, Rubagotti A, Guglilmini P, Porpiglia M, Mesiti M, Rinaldini M, Paldini G, Distante V, Franchi R, Soto PH, Buzzi F, Massidda B, Amadori D, Sismondi P, Cruciani G, Farris A. Switching to anastrozole (ANA) vs continued Tamoxifen (TAM) treatment of early breast cancer (EBC). Updated results of the Italian Tamoxifen Anastrozole (ITA) trial. European Journal of Cancer Supplements 2005;3(1):35, Abs O-111