Scottish Medicines Consortium

anastrozole 1mg tablets (Arimidex®) No. (198/05)

AstraZeneca UK Ltd

New indication: for adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer

5th August 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

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.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Anastrozole 1mg tablets (Arimidex®)

Licensed indication under review

For adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer.

(Previous licence restricted use to those unable to take tamoxifen because of high risk of thromboembolism or endometrial abnormalities. Anastrozole is also licensed for the treatment of advanced disease in postmenopausal women).

Dosing information under review

One 1mg tablet daily. For early disease the recommended duration of treatment is 5 years.

UK launch date

June 2005

Comparator medications

The only other agent licensed for use in early disease is tamoxifen.

Cost per treatment period and relevant comparators

Drug	Dose	Annual cost (£)*	5-year cost (£)*
Anastrozole (Arimidex®)	1mg daily	894	4469
Tamoxifen (generic)*	20mg daily	24	121
Tamoxifen (Nolvadex-D®)	20mg daily	106	530

* costs from eVadis drug dictionary accessed in June 2005.

Summary of evidence on comparative efficacy

The management of patients with breast cancer involves a combination of surgery, radiotherapy and drug therapy. Drug therapy includes cytotoxic chemotherapy and, for patients with oestrogen-receptor [ER]-positive tumours, adjuvant drugs including tamoxifen are given to eradicate micrometastases that cause recurrences. Tamoxifen is an oestrogen receptor antagonist licensed in the treatment of ER-positive breast cancer in both pre- and post-menopausal women. It also has 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. Anastrozole is an aromatase inhibitor, drugs which act predominantly by blocking peripheral conversion of androgens to oestrogens. They do not inhibit ovarian oestrogen synthesis and should not be used in the treatment of pre-menopausal women. This submission focuses on a licence extension to include early disease treatment in post-menopausal women.

The key data to support this is the Arimidex, Tamoxifen Alone or in Combination (ATAC) study. Results of this study have been reported after a median of 33 months, 47 months and more recently after 68 months. The company submission focused on this most recent analysis. The study enrolled postmenopausal women with histologically proven operable invasive breast cancer who had completed primary surgery and chemotherapy/radiotherapy (where given) and were considered eligible for hormonal adjuvant therapy. Patients were randomised to receive anastrozole (1mg daily), tamoxifen (20mg daily) or a combination of the two drugs, treatment continuing for five years. The combination arm was discontinued when the analysis at 33 and 47 months showed no treatment advantage.

The primary study endpoint was disease-free survival, defined as the time to the earliest occurrence of local or distant recurrence, new primary breast cancer or death from any cause. After a median follow-up of 68 months, disease free survival was significantly improved with anastrozole compared to tamoxifen, with 575 and 651 patients respectively experiencing an event; that is 82% anastrozole and 79% tamoxifen patients remaining disease-free, representing an absolute risk reduction for any event of 2.5%. This advantage was greater in patients with hormone-receptor-positive disease (p=0.005).

Secondary endpoints of time to recurrence, incidence of new contralateral breast tumours and distant recurrence also significantly favoured anastrozole over tamoxifen. The relative reductions of each of these endpoints were greater in the subgroup with hormone receptor-positive disease. There was no significant difference in time to breast cancer death and overall survival at the 68 months follow-up.

The trial included four sub-protocols of which two were concerned with efficacy and two with safety. One of these investigated quality of life outcomes in the first two years of treatment for 1021 patients using a Functional Assessment of Cancer Therapy - Breast questionnaire with an endocrine sub-scale. Overall, it found no difference between anastrozole and tamoxifen in a treatment outcome index which was a composite score from the physical and functional well-being scales and the breast cancer sub-scales of the questionnaire and which improved marginally from baseline in all groups. There was a decline on the endocrine sub-scale which was not significantly different between anastrozole and tamoxifen and which stabilised after 3 months. The conclusion was that there was no detrimental impact of anastrozole on quality of life. This was supported by a recent 5-year update.

Summary of evidence on comparative safety

Compared with anastrozole, tamoxifen was associated with a significantly greater incidence of hot flushes (41% vs 36%, p<0.0001), vaginal bleeding (10% vs 5.4%, p<0.0001) and discharge (13% vs 3.5%, p<0.0001), ischaemic cerebrovascular events (2.8% vs 2.0%, p=0.03), and venous thromboembolic events (4.5% vs 2.8%, p=0.0004) including deep venous events (2.4% vs 1.6%, p=0.02). Tamoxifen was associated with a greater incidence of endometrial malignancies (0.8% vs 0.2%, p=0.02). In a sub-protocol of ATAC, 279 patients were enrolled to evaluate treatment effects on endometrial status following two years of treatment. There was a non-significant reduction in the number of endometrial abnormalities for the anastrozole arm compared with the tamoxifen arm (9% vs 17%, p=0.18). Atypical hyperplasia, a possible malignant precursor, occurred de novo in 1.9% of patients taking tamoxifen and none of the patients in this sub-protocol taking anastrozole. A retrospective analysis of ATAC at 68 months follow-up found significantly fewer gynaecological adverse events with anastrozole (20% vs 34%, p<0.0001).

Anastrozole was associated with a significantly greater incidence of musculoskeletal disorders (36% vs 29%, p<0.0001) and fractures (11% vs 7.7%, p<0.0001) than tamoxifen. In

another sub-protocol, effects on bone mineral density (BMD) and bone biomarkers were investigated in 308 patients at one year. Anastrozole was associated with bone loss at the spine and hip and an increase in markers of bone turnover, and this may have contributed to the increased risk of fractures observed. Tamoxifen was associated with an increase in BMD and a reduction in markers of bone turnover.

Summary of clinical effectiveness issues

While anastrozole demonstrated benefits over tamoxifen in terms of disease-free survival, no significant difference in the overall survival between treatments was found on the latest analysis. However it is acknowledged that a longer follow-up may be required to assess this as with tamoxifen. The latest report from the Early Breast Cancer Trialists' Collaborative Group (EBCTG) indicates that tamoxifen, given for about five years as adjunctive therapy to women with early breast cancer of hormone receptor-positive or -unknown status, is associated with a breast cancer mortality rate of 26% at 15 years compared to 35% in the control group. The effects of tamoxifen on mortality have been shown to continue after stopping therapy at 5 years. Further follow-up will determine whether anastrozole will be similar.

In the ATAC trial, the treatment differences between anastrozole and tamoxifen are in addition to the expected treatment differences between tamoxifen and no treatment. For example in EBCTG, 5 years' tamoxifen in women with oestrogen receptor-positive or -unknown status was associated with an absolute reduction in recurrence of 11% after 5 years follow-up, 14% after 10 years and 22% after 15 years.

Differences in the adverse events profile between tamoxifen and anastrozole may reflect the partial oestrogen agonist properties of the former. Some adverse events associated with anastrozole may reflect relative deficiency of oestrogen, e.g. its effects on bone. The summary of product characteristics states that women with osteoporosis or at risk of osteoporosis should have their bone mineral density assessed by bone densitometry at the start of treatment and regularly during treatment.

Summary of comparative health economic evidence

A 7-state cost-utility Markov model was presented over a 25-year time horizon, which compared anastrozole with tamoxifen.

The main data source for the clinical data was the ATAC study discussed in the comparative efficacy section, for which an analysis was performed when the median follow up time was 68 months. For the base case analysis it was assumed that anastrozole continued to show incremental benefit over tamoxifen, up to 10 years from initiation of treatment. A Weibull regression model was used to extrapolate the data beyond the 5-year time horizon.

The strengths of the model were the use of reputable sources for the resource use and the comprehensive sensitivity analyses. One main weakness within the model was that weighted utilities based on adverse events were computed and adverse events rates were assumed to be the same for each three month period. This may not be realistic and may potentially overestimate the QALY gain and therefore underestimating the incremental cost per QALY. Possible costs to healthcare systems of screening for and treating osteopenia/osteoporosis in patients receiving anastrozole may have been underestimated in the model.

The base case results showed a cost of £7811 per QALY for treatment with anastrozole compared to treatment with tamoxifen. The sensitivity analyses showed that the results of the model were robust to changes in key parameters and assumptions. An analysis examined the key base-case assumption of an extension of recurrence benefits for anastrozole up to 10 years from start of treatment. In the short-term scenario, the recurrence benefit was limited to 68 months and the resulting ICER was £14,258/QALY. In the long-term scenario, the benefit was assumed to extend to the lifetime of the patient, ie 25 years, reducing the ICER to £4,693/QALY.

Patient and Public involvement

Patient Interest Group Submission: Breast Cancer Care Scotland.

Budget impact

The manufacturer estimated a net drug budget impact based on anastrozole use in 15% of newly diagnosed early breast cancer patients in year 1 (estimated cost - £256,000) increasing to 35% uptake in 2009 (estimated cost - £1.8m). It should be noted that other costs to the service in terms of screening and management of osteopenia / osteoporosis have not been considered in this estimate.

Guidelines and protocols

SIGN Guideline No.29 (1998)

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

SMC issued advice in February 2004 on the anastrozole licence extension to include adjunctive treatment of postmenopausal women with oestrogen receptor-positive early invasive breast cancer who are unable to take tamoxifen beacause of a high risk of thromboembolism or endometrial abnormalities. Anastrozole was recommended for restricted use in such women 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. Treatment with anastrozole should be initiated by an oncologist. Tamoxifen continues to be the first line treatment for early breast cancer where it is not contra-indicated for the reasons above.

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 July 2005.

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.

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Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687-1717.

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