

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer

This guidance applies to the use of the aromatase inhibitors anastrozole, exemestane and letrozole, within the marketing authorisations for each drug at the time of this appraisal for the treatment of early oestrogen-receptor-positive breast cancer; that is:

- anastrozole for primary adjuvant therapy
- exemestane for adjuvant therapy following 2–3 years of adjuvant tamoxifen therapy
- letrozole for primary adjuvant therapy and extended adjuvant therapy following standard tamoxifen therapy.

1 Guidance

- 1.1 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.
- 1.2 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.

2 Clinical need and practice

- 2.1 Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue. It is the most common type of cancer among women in the UK. The incidence of breast cancer in England and Wales in 2003 was 38,864, accounting for approximately 30% of all reported cancers in women. The age-standardised incidence rates in England and Wales are 144 and 113 per 100,000 population respectively, and women have a one in nine lifetime risk of developing breast cancer. Breast cancer is also the most common cause of cancer-related deaths in women. Approximately 10,500 women died from breast cancer in England in 2003.
- 2.2 Breast cancer incidence increases with age, and around 80% of breast cancers occur in women older than 50. Factors associated with increased breast cancer risk include previous breast cancer, early menarche, late menopause, hormone replacement therapy, oral contraception, obesity and alcohol consumption. It is also thought that breast cancer risk is increased in women who have not had children, or had children late, and women who have not breast-fed a baby. Family history and genetic predisposition also play an important role, because women who possess mutations of breast cancer susceptibility genes (BRCA1 or 2) are at a higher risk of developing breast cancer. However, the majority of breast cancers occur in women with no direct family history of the disease.
- 2.3 Once breast cancer is diagnosed, prognosis and treatment decisions depend on the extent of the disease. This is assessed by tumour staging, based on the size and nature of the primary tumour, the involvement of the regional lymph nodes and the presence of distant metastases. When the cancer remains localised in the breast ductules it is known as ductal carcinoma in situ (DCIS), or stage 0 of the Union Internationale Contre le Cancer (UICC) tumour, node, metastases (TNM) clinical staging system. Stages 1 to 3 of the UICC TNM clinical staging system describe cancer that has spread locally to the breast tissue and possibly the lymph glands in the armpit. If the cancer

has spread to these local lymph glands, or nodes, it is called 'node-positive'. Stage 4 describes cancer in which the cancer cells have spread through the bloodstream and lymphatic system to other parts of the body. In stages 1 and 2 the tumour is smaller than 5 cm, and these stages are known as early breast cancer.

- 2.4 Breast tissue contains receptors for the female hormones oestrogen and progesterone. These receptors allow the breast tissue to grow or change in response to changing levels of those hormones. Approximately two thirds of women diagnosed with breast cancer have hormone-receptor-positive tumours; oestrogen or progesterone are the main hormones involved in the development and growth of this type of breast cancer. Hormone-receptor-positive tumours also tend to grow less aggressively, resulting in a better prognosis.
- 2.5 Current treatment options for early breast cancer depend on disease characteristics (such as stage and hormone-receptor status of the tumour), on patient characteristics (such as age and menopausal status) and on personal preferences.
- 2.6 Treatment can be divided into surgical treatment and adjuvant treatment after surgical removal of the primary cancer. The purpose of surgery is to control the disease locally (within the breast and axillary lymph nodes) and to determine the prognostic characteristics of the primary cancer. Adjuvant treatment may involve radiotherapy, chemotherapy, hormone therapy or molecular targeted therapy. The aim of adjuvant treatment is to prevent recurrence.
- 2.7 The aim of hormonal therapy is to deprive the tumour cells of the proliferative stimulus provided by oestrogen. This can be achieved by blocking the binding of oestrogen to its receptor in the nucleus of responsive cells, as with tamoxifen. In the UK, 5 years of tamoxifen therapy has become standard adjuvant hormonal treatment for postmenopausal women with early

oestrogen-receptor-positive breast cancer. Tamoxifen also provides protection against bone fractures in postmenopausal women and it lowers serum cholesterol levels. However, long-term use of tamoxifen may be associated with vaginal bleeding, endometrial thickening, and increased risk of endometrial cancer and thromboembolic events.

3 The technologies

- 3.1 In premenopausal women, oestrogens are directly produced in the ovaries until production declines during the menopause. After the menopause oestrogens are still produced (to a lesser extent) in non-ovarian tissues such as muscle and fat by the enzyme aromatase, which converts androgens secreted by the adrenal cortex into oestrogens.
- 3.2 Aromatase inhibitors act by blocking the conversion of androgens to oestrogens in the peripheral tissues in postmenopausal women, thereby reducing the circulating levels of oestrogens.
- 3.3 Three aromatase inhibitors have UK marketing authorisation for the adjuvant treatment of early oestrogen-receptor-positive breast cancer in postmenopausal women: anastrozole, exemestane and letrozole.
- 3.4 Because aromatase inhibitors reduce circulating oestrogen levels, a decrease in bone mineral density can be anticipated. Therefore, a warning has been included in the summaries of product characteristics of all three aromatase inhibitors that women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the beginning of treatment and, for anastrozole, at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and patients treated with an aromatase inhibitor should be carefully monitored.

- 3.5 Further side effects and contraindications are associated with individual aromatase inhibitors. For full details of side effects and contraindications see the summaries of product characteristics.

Anastrozole

- 3.6 Anastrozole (Arimidex; AstraZeneca UK) is a reversible, non-steroidal aromatase inhibitor. At the time of this appraisal, it was licensed in the UK for adjuvant treatment of postmenopausal women with early hormone-receptor-positive invasive breast cancer. At the time of this appraisal, it was also licensed for the treatment of advanced breast cancer in postmenopausal women.
- 3.7 For early disease the recommended duration of treatment with anastrozole is 5 years. The recommended dose of anastrozole is one 1-mg tablet to be taken orally once daily.
- 3.8 The acquisition cost of anastrozole 1-mg tablets is £68.56 for 28 (excluding VAT; 'British national formulary' 51st edition [BNF 51], March 2006). Costs may vary in different settings because of negotiated procurement discounts.

Exemestane

- 3.9 Exemestane (Aromasin; Pfizer) is an irreversible steroidal aromatase inhibitor. It is licensed in the UK for the adjuvant treatment of postmenopausal women with oestrogen-receptor-positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy. It is also licensed for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.
- 3.10 In women with early breast cancer, treatment with exemestane should continue until completion of 5 years of combined sequential adjuvant hormonal therapy (tamoxifen followed by exemestane) or until tumour relapse

occurs, whichever comes first. The recommended dose of exemestane is one 25-mg tablet to be taken orally once daily.

- 3.11 The acquisition cost of exemestane 25-mg tablets is £88.80 for 30 and £266.40 for 90 (excluding VAT; BNF 51). Costs may vary in different settings because of negotiated procurement discounts.

Letrozole

- 3.12 Letrozole (Femara; Novartis Pharmaceuticals UK) is a reversible, non-steroidal aromatase inhibitor. It is licensed in the UK for the adjuvant treatment of postmenopausal women with hormone-receptor-positive invasive early breast cancer, and for the treatment of postmenopausal women with hormone-receptor-positive invasive early breast cancer who have already received standard adjuvant tamoxifen therapy for 5 years. Letrozole is also licensed in the UK for various indications in advanced breast cancer and as neo-adjuvant treatment.

- 3.13 Adjuvant treatment with letrozole should continue for 5 years or until tumour relapse occurs, whichever comes first. Following standard adjuvant tamoxifen therapy, treatment with letrozole should continue for 3 years or until tumour relapse occurs, whichever comes first. The recommended dose of letrozole is one 2.5-mg tablet to be taken orally once daily.

- 3.14 The acquisition cost of letrozole 2.5-mg tablets is £83.16 for 28 (excluding VAT; BNF 51). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group identified seven prospective randomised controlled trials (RCTs) that it considered to meet the inclusion criteria. Anastrozole was investigated in four studies, letrozole in two studies, and exemestane in one study.

4.1.2 Each study examined one of four different treatment strategies:

- primary adjuvant treatment (that is, participants were randomised, following surgery to remove the primary cancer, to receive an aromatase inhibitor or tamoxifen for 5 years)
- planned switch treatment (that is, participants were randomised, following surgery to remove the primary cancer, to receive tamoxifen for 5 years or tamoxifen for 2 to 3 years followed by an aromatase inhibitor for 2 to 3 years)
- unplanned switch treatment (that is, participants were randomised, after 2 to 3 years of adjuvant tamoxifen therapy, to receive 2 to 3 years of an aromatase inhibitor or another 2 to 3 years of tamoxifen therapy)
- extended adjuvant treatment (that is, participants were randomised, after 5 years of adjuvant tamoxifen therapy, to receive 3 years of an aromatase inhibitor or placebo).

4.1.3 Meta-analysis of the RCTs was not possible because of the heterogeneity of trial designs.

4.1.4 In addition to the RCTs outlined in sections 4.1.1 and 4.1.2, two secondary studies were identified that compared anastrozole with tamoxifen in women who had already undergone 2 to 3 years of adjuvant tamoxifen therapy.

Anastrozole

4.1.5 The largest study of anastrozole (n = 9366) compared 5 years of anastrozole as primary adjuvant treatment with 5 years of tamoxifen, and with 5 years of

anastrozole and tamoxifen in combination in women with hormone-receptor-positive or -negative disease. The trial investigators reported that the arm receiving the combination of anastrozole and tamoxifen was closed early because of low efficacy. The data were analysed on an intention-to-treat basis (data not presented here) and separately for the subgroup of women with hormone-receptor-positive disease. The median follow-up in this study was 68 months.

- 4.1.6 Anastrozole was associated with a statistically significant increase in disease-free survival compared with tamoxifen. Among the population of women in the study with hormone-receptor-positive disease, 80.9% were alive and disease-free in the tamoxifen group and 83.8% in the anastrozole group (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.73 to 0.94).
- 4.1.7 The study found no statistically significant differences in overall survival between treatment groups. In the tamoxifen group 11.6% of participants with hormone-receptor-positive disease died, compared with 11.3% in the anastrozole group (HR 0.97, 95% CI 0.83 to 1.14). There were also no statistically significant differences between treatment groups in breast-cancer-related survival. In the tamoxifen group 6.6% of participants with hormone-receptor-positive disease died following a cancer event, compared with 5.8% in the anastrozole group (HR 0.87, 95% CI 0.70 to 1.09).
- 4.1.8 For breast cancer recurrence a statistically significant difference between treatment groups was reported. In the tamoxifen group this recurrence affected 14.2% of participants with hormone-receptor-positive disease, compared with 10.8% in the anastrozole group (HR 0.74, 95% CI 0.64 to 0.87). Contralateral breast cancer was experienced by 2.0% of participants in the tamoxifen group with hormone-receptor-positive disease and 1.0% in the anastrozole group (odds ratio [OR] 0.47, 95% CI 0.29 to 0.75). Distant recurrence as a first event was experienced by 10.2% of participants in the tamoxifen group with hormone-receptor-positive disease compared with 8.6% in the anastrozole group (HR 0.84, 95% CI 0.70 to 1.00).

- 4.1.9 For adverse events, the study reported a higher risk of bone fracture with anastrozole compared with tamoxifen: 7.7% of participants in the tamoxifen group overall experienced a fracture compared with 11.0% in the anastrozole group (OR 1.49, 95% CI 1.25 to 1.77). However, the OR for hip fracture – the fracture type most frequently associated with mortality – was not statistically significant (OR 1.20, 95% CI 0.74 to 1.93).
- 4.1.10 No statistically significant differences between treatment arms were reported for ischaemic cardiovascular disease. However, in the anastrozole arm there were statistically significantly fewer ischaemic cerebrovascular events, venous thromboembolic events and deep venous thromboembolic events overall compared with the tamoxifen arm. The ORs for each type of event were 0.70 (95% CI 0.50 to 0.97), 0.61 (95% CI 0.47 to 0.80), and 0.64 (95% CI 0.45 to 0.93), respectively.
- 4.1.11 Anastrozole was also associated with a lower risk of endometrial cancer compared with tamoxifen: 0.8% of participants overall developed endometrial cancer in the tamoxifen arm compared with 0.2% in the anastrozole group (OR 0.29, 95% CI 0.11 to 0.80). Rates of vaginal bleeding and hysterectomy were also higher overall in the tamoxifen group.
- 4.1.12 Quality of life was assessed in 11% of the participants randomised in the study using two disease-specific instruments. No statistically significant differences in the primary or secondary endpoints were identified across treatment groups.
- 4.1.13 Three other studies of anastrozole investigated its use in contexts that were outside its licensed indications at the time of this appraisal (that is, as part of a planned switch treatment, unplanned switch therapy or extended adjuvant therapy). Therefore, the results of these studies are not presented.

Exemestane

4.1.14 The Assessment Report identified one study (n = 4742) that compared exemestane with tamoxifen in women who had already undergone 2 to 3 years of adjuvant tamoxifen therapy. The results in the Assessment Report were based on published data, at a median follow-up of 31 months, and on data from a conference presentation covering fewer outcomes at a median follow-up of 37 months.

4.1.15 Exemestane was associated with a statistically significant increase in disease-free survival compared with tamoxifen: in the tamoxifen group, at a median follow-up of 37 months, 85.1% of participants were alive and disease-free compared with 89.0% in the exemestane group (HR 0.73, 95% CI 0.62 to 0.86).

4.1.16 No statistically significant differences in overall survival between treatment groups were found either at 31 months or at 37 months follow-up. In the tamoxifen group, at a median follow-up of 37 months, 7.9% of participants had died compared with 6.4% in the exemestane group (HR 0.83, 95% CI 0.67 to 1.02). However, there was a statistically significant difference in breast-cancer-related survival, reported at a median follow-up of 31 months, favouring exemestane (HR 0.63, 95% CI 0.51 to 0.77).

4.1.17 For breast cancer recurrence a statistically significant difference between treatment groups was reported. In the tamoxifen group, at a median follow-up of 37 months, disease recurred in 12.2% of participants compared with 8.7% in the exemestane group (HR 0.70, 95% CI 0.58 to 0.83). In addition, the study found a statistically significant difference in the rate of contralateral breast cancer. At a median follow-up of 37 months this was experienced by 1.1% of participants in the tamoxifen group and 0.5% in the exemestane group (HR 0.50, 95% CI 0.26 to 0.97). At a median follow-up of 31 months differences between treatment groups in distant recurrence were also

statistically significant, favouring exemestane (HR 0.66, 95% CI 0.52 to 0.83; event rates not given).

4.1.18 For adverse events, at a median follow-up of 31 months, there was a higher risk of bone fracture with exemestane compared with tamoxifen (2.3% of participants in the tamoxifen group experienced a fracture compared with 3.1% in the exemestane group). However, it is not clear whether this is statistically significant (HR and 95% CI not given). There was statistically significantly more thromboembolic disease and thromboembolic events in the tamoxifen arm ($p = 0.003$ and $p = 0.007$ respectively). The study also found higher incidences in the tamoxifen group of endometrial cancer (affecting 0.5% of participants versus 0.2%) and of vaginal bleeding (affecting 5.5% of participants versus 4.0%; HR and 95% CI not given).

4.1.19 Quality of life was assessed in a substudy comprising 12% of the participants randomised in the main study using a cancer-specific instrument with an endocrine symptom subscale. No statistically significant differences in the primary or secondary endpoints were identified across treatment groups, except for vaginal discharge (tamoxifen 7.8%; exemestane 1.4%; $p = 0.002$).

4.1.20 The Institute received longer follow-up data for this study (median 56 months) from the manufacturer. The HR for overall survival, adjusted for nodal status, chemotherapy use and use of hormone replacement therapy, for women with oestrogen-receptor-positive disease and women with unknown receptor status, was 0.83, 95% CI 0.69 to 0.99, favouring exemestane. Statistically significant differences favouring exemestane, for women with oestrogen-receptor-positive disease and women with unknown receptor status, were also reported for disease-free survival (HR 0.75, 95% CI 0.65 to 0.87), breast-cancer-free survival (HR 0.75, 95% CI 0.64 to 0.87), time to distant recurrence (HR 0.82, 95% CI 0.69 to 0.98) and time to contralateral breast cancer (HR 0.56, 95% CI 0.33 to 0.98). For adverse events there was a higher overall incidence of bone fracture with exemestane compared with tamoxifen (7.0% versus 4.9%; $p = 0.003$). In the tamoxifen arm there was a

higher incidence of thromboembolic events (3.1% versus 1.9%; $p = 0.01$) and of serious gynaecological adverse events (9.8% versus 6.4%; $p < 0.001$).

Letrozole

4.1.21 One of the two studies of letrozole identified ($n = 8010$) compared two primary adjuvant and two sequencing strategies:

- a) 5 years of tamoxifen
- b) 5 years of letrozole
- c) 2 years of tamoxifen followed by 3 years of letrozole
- d) 2 years of letrozole followed by 3 years of tamoxifen.

Results were based on an analysis combining all women initially treated with tamoxifen (arms a and c) and all women initially treated with letrozole (arms b and d) at a median follow-up of 26 months.

4.1.22 Letrozole was associated with a statistically significant increase in disease-free survival from 89.3% of participants in the tamoxifen group being alive and disease-free to 91.2% in the letrozole group (HR 0.81, 95% CI 0.70 to 0.93).

4.1.23 The study found no statistically significant differences in overall survival between treatment groups. In the tamoxifen group 4.8% of participants died, compared with 4.1% in the letrozole group (HR 0.86, 95% CI 0.70 to 1.06). For breast-cancer-related survival, 3.8% of participants in the tamoxifen group died following a cancer event compared with 2.8% in the letrozole group (HR and 95% CI not given).

4.1.24 For breast cancer recurrence, a statistically significant difference between treatment groups was reported. In the tamoxifen group 7.7% of participants relapsed compared with 5.6% in the letrozole group (HR 0.72, 95% CI 0.61 to 0.88). Differences between treatment groups in distant recurrence were also statistically significant. In the tamoxifen group 5.8% of participants experienced distant recurrence, compared with 4.4% in the letrozole group

(HR 0.73, 95% CI 0.60 to 0.88). Contralateral breast cancer was experienced by 0.7% of participants in the tamoxifen group and 0.4% of participants in the letrozole group (HR and 95% CI not given).

4.1.25 For adverse events, the study reported a higher risk of bone fracture with letrozole compared with tamoxifen (4.0% of participants in the tamoxifen group experienced a fracture compared with 5.7% in the letrozole group; HR and 95% CI not given). A higher risk of developing hypercholesterolaemia with letrozole was also reported. This affected 19.2% of participants in the tamoxifen group compared with 43.6% in the letrozole group (HR and 95% CI not given).

4.1.26 No statistically significant differences between treatment arms were reported for ischaemic heart disease or cardiac events overall. However, there were statistically significantly fewer thromboembolic events in the letrozole arm (1.5% versus 3.5%; $p < 0.001$), but a greater risk of grade 3 to 5 cardiac events (2.1% versus 1.1%; $p < 0.001$). Letrozole was associated with a statistically significant increase in the rate of cardiac failure (0.8% in the letrozole group versus 0.4% with tamoxifen; $p = 0.01$) and in 'other cardiac events' (0.5% in the letrozole group versus 0.2% with tamoxifen; $p = 0.04$).

4.1.27 Rates of invasive endometrial cancer were similar between the two groups (0.3% in the tamoxifen group versus 0.1% with letrozole; $p = 0.18$), but rates of vaginal bleeding were higher in the tamoxifen group (affecting 6.6% of participants versus 3.3% with letrozole; p -value and 95% CI not given). Quality of life data were not reported.

4.1.28 The second study of letrozole ($n = 5187$) was designed to compare an extended adjuvant strategy of 5 years of letrozole with placebo in women who had survived disease-free after 5 years of primary adjuvant treatment with tamoxifen. The study was stopped early because it reached its predetermined endpoint in advance of the expected timeframe. The median follow-up in this study was 30 months.

- 4.1.29 No statistically significant differences in overall survival between treatment groups were reported. In the placebo group 2.4% of participants died compared with 2.0% in the letrozole group (HR 0.82, 95% CI 0.57 to 1.19). For breast-cancer-related survival, 0.9% of participants in the placebo group died following a cancer event compared with 0.6% in the letrozole group (HR and 95% CI not given).
- 4.1.30 For breast cancer recurrence a statistically significant difference between treatment groups was reported. Disease recurred in 6.0% of participants in the placebo group and 3.6% in the letrozole group (HR 0.58, 95% CI 0.45 to 0.76). The study found no statistically significant difference in the rate of contralateral breast cancer, which was experienced by 1.1% of participants in the placebo group and 0.7% in the letrozole group (HR 0.63, 95% CI 0.18 to 2.21). However, differences between treatment groups in distant recurrence were statistically significant. Distant recurrence affected 3.6% of participants in the placebo group and 2.2% in the letrozole group (HR 0.60, 95% CI 0.43 to 0.84).
- 4.1.31 For adverse events, the study found no statistically significant differences in fracture risk between treatment groups (4.6% of participants in the placebo group versus 5.3% in the letrozole group experienced a fracture; $p = 0.25$). Rates of cardiovascular events were also similar between treatment groups, affecting 5.6% and 5.8% of participants in the placebo and letrozole groups respectively ($p = 0.76$). In the placebo group 0.4% of participants developed endometrial cancer compared with 0.2% in the letrozole group, and 7.6% and 5.6% respectively experienced vaginal bleeding. No statistically significant differences in rates of hypercholesterolaemia were reported (15.9% in the placebo group versus 16.3% in the letrozole group). HRs and 95% CIs were not given.
- 4.1.32 Quality of life was assessed in a substudy comprising 70% of the participants randomised in the main study, using the Short Form 36 (SF-36) generic instrument and the Menopause-Specific Quality of Life questionnaire

(MENQOL). The SF-36 results showed no statistically significant differences for the summary scores, but statistically significant differences favouring placebo were identified for physical function ($p = 0.011$), bodily pain ($p = 0.009$) and general health ($p = 0.034$). A statistically significant difference, favouring placebo, was also identified on the physical ($p = 0.04$) and vasomotor scales ($p < 0.001$) of the MENQOL questionnaire.

Additional evidence from professional and patient groups

4.1.33 In their submissions, patient organisations pointed out that menopausal symptoms (such as hot flushes and vaginal bleeding) are experienced less frequently with aromatase inhibitors than with tamoxifen. They expressed the view that this was very important to the quality of life of many women undergoing cancer treatment.

4.1.34 The professional groups expressed the view that the choice of hormonal treatment should depend on risk of recurrence.

Summary of clinical evidence

4.1.35 There is consistent evidence from RCTs that, relative to tamoxifen, aromatase inhibitors improve clinical outcomes when used within their licensed indications as primary adjuvant treatment, in unplanned switching or as extended adjuvant treatment. The clinical trials also illustrate the different side-effect profiles of aromatase inhibitors and tamoxifen, with higher rates of bone fracture evident with aromatase inhibitors, and greater risk of endometrial cancer and other gynaecological conditions with tamoxifen. There is little evidence from the trials of any difference in quality of life as a result of taking an aromatase inhibitor compared with tamoxifen.

4.2 Cost effectiveness

4.2.1 The Assessment Group reviewed the literature and the submitted economic evidence, and generated its own economic model.

- 4.2.2 One cost-effectiveness study of anastrozole from the US was identified, which did not include endometrial cancer as an outcome, and it included a 25% reduction in benefit for anastrozole because of the effect on hip fracture. This was associated with an incremental cost per quality-adjusted life year (QALY) of \$76,000 over a 20-year horizon or \$202,000 over an 8-year horizon.
- 4.2.3 Economic models were submitted by the manufacturers of each drug for use in primary adjuvant, unplanned switch and extended adjuvant treatments, as appropriate. All submitted models were Markov models with 1000 simulations, a mean patient age of 61–64 years and a 25-year or lifetime horizon, and they all contained broadly similar health states and model structures. Differences between the models included the assumptions on the duration of benefit, the source of the utility data, and the inclusion of adverse events. The individual models were based on the data from the relevant clinical studies.
- 4.2.4 The Assessment Group developed a probabilistic Markov model that used trial evidence for all three treatment strategies and drugs separately, and five sub-models were developed: anastrozole (primary adjuvant and unplanned switch, the latter being an unlicensed indication), letrozole (primary adjuvant and extended adjuvant) and exemestane (unplanned switch). Health-related utilities were taken from published literature. The model used an annual cycle length and was run until patients reached 100 years of age. The comparator for the primary adjuvant and the unplanned switch strategies was 5-year tamoxifen therapy immediately following surgery, and for extended adjuvant therapy was placebo. The health states modelled were disease-free survival, loco-regional or contralateral recurrence, remission from loco-regional or contralateral recurrence, distant recurrence, death from breast cancer (via metastatic disease) and death from other causes.
- 4.2.5 An important assumption in the model was related to the duration of benefit after the treatment period: in the base-case analysis the benefits of aromatase inhibitors, in terms of relative risk, gradually declined over the next 10-year period to the extent that, by year 15 after surgery, the number of

patients in disease-free survival was the same in both arms. The Assessment Group considered this to be a conservative assumption. An alternative assumption was tested in a sensitivity analysis (referred to as 'benefits maintained'). In the 'benefits maintained' scenario the rate of recurrence was the same for both arms after the treatment period, based on a long-term follow-up study on tamoxifen, thereby preserving the benefits of aromatase inhibitors.

- 4.2.6 The following adverse events of tamoxifen were included in the model: vaginal bleeding, endometrial cancer, venous thromboembolic events and ischaemic cerebrovascular disorders. Hypercholesterolaemia was excluded as an adverse event in the model because of the current uncertainty in the evidence base. Cardiovascular events were not modelled. Although the effect of aromatase inhibitors on hip fracture was not statistically significant, it was included in the model because of the potential long-term risks of hip and other fractures in postmenopausal women. The impact of fracture on the cost effectiveness was modelled separately using the Assessment Group's model developed for the appraisal on bisphosphonates, raloxifene, strontium ranelate and teriparatide for the prevention of osteoporotic fractures. The base case included a differential effect on fracture between treatment arms extending 5 years beyond the treatment period, with the relative risk for fracture being constant during the time of endocrine therapy, and declining gradually to control level over the next 5 years. The impact of doubling the fracture risk, a constant fracture risk over 10 years and the addition of treatment for osteoporosis with bisphosphonates was also estimated.
- 4.2.7 Generally, treatment with aromatase inhibitors was associated with increased drug costs and slightly decreased follow-up costs (for example, the costs of treating disease recurrence) compared with tamoxifen. Adverse events made a very minor contribution to the costs.
- 4.2.8 For primary adjuvant treatment the Assessment Group's modelling of 5-year treatment with anastrozole compared with 5-year tamoxifen was associated

with incremental costs per QALY gained of £31,965 and £12,310, using the base-case assumptions on the duration of benefit and the 'benefits maintained' scenario respectively. The corresponding result for anastrozole from the submission model was £12,463 for an analysis similar to the 'benefits maintained' scenario. The Assessment Group's modelling of 5-year treatment with letrozole compared with 5-year treatment with tamoxifen was associated with incremental costs per QALY gained of £21,580 and £9325, using the base-case assumptions on the duration of benefit and the 'benefits maintained' scenario respectively. The corresponding result for letrozole from the submission model was £10,286 for an analysis similar to the 'benefits maintained' scenario. Because of the shorter follow-up in the letrozole study underpinning this modelling, the results for letrozole were associated with a higher uncertainty than the results for anastrozole.

4.2.9 For unplanned switching the Assessment Group's modelling of 2- to 3-year tamoxifen therapy followed by a 2- to 3-year treatment with exemestane (compared with 5-year tamoxifen therapy) was associated with incremental costs per QALY gained of £19,170 using the base-case assumption on the duration of benefit, and £1638 using the 'benefits maintained' scenario – the latter value being lower than the corresponding result from the manufacturer's submission. The results from the model that compared anastrozole and tamoxifen in unplanned switching are not included because they relate to the use of anastrozole outside its licensed indication at the time of the appraisal.

4.2.10 For extended adjuvant treatment the Assessment Group's base-case analysis of 5 years of treatment with letrozole after 5 years of tamoxifen therapy was associated with an incremental cost per QALY gained of £9760 when compared with 5-year tamoxifen therapy followed by placebo. When the 'benefits maintained' scenario was used the incremental cost per QALY gained was £3306. The corresponding result from the manufacturer's submission was £7725 for an analysis similar to the 'benefits maintained' scenario.

- 4.2.11 When alternative assumptions on the impact of increased fracture risk and treatment for osteoporosis were included in the Assessment Group's model the incremental cost per QALY gained increased to more than £35,000 for anastrozole used as primary adjuvant treatment. However, using these assumptions in the 'benefits maintained' scenario the incremental cost per QALY gained remained less than £20,000 for all drugs and treatment strategies.
- 4.2.12 The manufacturer's model for letrozole in extended adjuvant treatment showed that the incremental cost-effectiveness ratios (ICERs) for node-negative and node-positive patients were £11,784 and £5373 respectively.
- 4.2.13 The Assessment Group carried out probabilistic sensitivity analyses for the base-case scenario, with the following results. For primary adjuvant treatment at a willingness to pay of £20,000 per additional QALY anastrozole and letrozole are 15–25% likely to be cost effective, while at a willingness to pay of £30,000 per additional QALY they are 50–60% likely to be cost effective. For unplanned switch treatment, exemestane is approximately 45% and 80% likely to be cost effective at a willingness to pay of £20,000 and £30,000 per additional QALY respectively. For extended adjuvant treatment letrozole is more than 95% likely to be cost effective at a willingness to pay of £20,000 per additional QALY. A probabilistic sensitivity analyses for the 'benefits maintained' scenario was not carried out. The probability of being cost effective can be expected to be higher with the 'benefits maintained' scenario.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer, having considered evidence on the nature of the condition and the value placed on the benefits of hormonal therapies by people with early oestrogen-receptor-positive breast cancer,

those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.3.2 The Committee considered the evidence on the clinical effectiveness of aromatase inhibitors. It noted that there were important differences among the clinical trials, particularly in the timing of treatment with an aromatase inhibitor in relation to any previous treatment with tamoxifen. Furthermore, the Committee was aware of the differences in the licensed indications among the aromatase inhibitors.
- 4.3.3 The Committee agreed that there is convincing evidence that all three aromatase inhibitors, within their respective licensed indications, provide clinical benefit over tamoxifen in primary adjuvant or unplanned switch treatment, and over placebo in extended adjuvant treatment. The Committee considered the differences between the clinical trials and agreed that there is insufficient evidence to conclude that any one aromatase inhibitor (used within the licensed indications) or treatment strategy is more clinically effective than another.
- 4.3.4 The Committee noted that aromatase inhibitors are associated with increased fracture risk. They may also be associated with increased cardiovascular risk compared with tamoxifen, but there is still uncertainty about the long-term adverse effects because of the short follow-up in most of the studies. The Committee also noted that tamoxifen, but not the aromatase inhibitors, is linked to an increased risk of endometrial cancer and other gynaecological conditions. The Committee heard from the patient experts that other side effects related to menopausal symptoms and general well-being, experienced with aromatase inhibitors or tamoxifen, can be unpredictable and vary considerably from one woman to another, having an important effect on quality of life. Therefore, the Committee accepted that tamoxifen and aromatase inhibitors are not necessarily interchangeable therapies for all women.

- 4.3.5 The Committee considered all the evidence on cost effectiveness of aromatase inhibitors and, in particular, the assumptions made on the duration of benefit after the treatment period. It heard from the clinical specialists that the 'benefits maintained' scenario, used by the Assessment Group in a sensitivity analysis, provides the most relevant analysis. This is because this assumption is biologically more plausible than the base-case assumption and can be inferred from the long-term follow-up data for tamoxifen compared with placebo. Therefore, the Committee based its discussion on the cost-effectiveness analysis using the 'benefits maintained' assumption, and it noted that the incremental cost per QALY gained for aromatase inhibitors, compared with tamoxifen, was less than £20,000 for all treatment strategies. It further noted that the incremental cost per QALY gained did not increase to more than £20,000 when the predicted fracture risk was increased. The Committee concluded that the licensed strategies for the use of the aromatase inhibitors are cost effective when individually compared with tamoxifen. It also agreed that in extended adjuvant treatment letrozole is cost effective compared with placebo.
- 4.3.6 The Committee was mindful of the fact that both anastrozole and letrozole are currently licensed for primary adjuvant treatment. However, because of the differences between the clinical trials, particularly in the length of follow-up, the Committee agreed that any comparison of cost effectiveness between anastrozole and letrozole was associated with considerable uncertainty. The Committee agreed that it would not be appropriate to differentiate between the two drugs for primary adjuvant treatment. Therefore, the Committee concluded that all three aromatase inhibitors, within their licensed indications, should be recommended as options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women.
- 4.3.7 The Committee considered the evidence relating to the clinical and cost effectiveness of aromatase inhibitors in different subgroups of women with

early breast cancer. It noted that the Assessment Report did not include any analysis of cost effectiveness in such subgroups but instead indicated that the use of aromatase inhibitors as primary adjuvant treatment was cost effective for the whole population of women with early breast cancer. The Committee noted that the recurrence rate of primary tumour is greatest for all women within the first 2 years after initial therapy and that, for women with node-positive cancer, this risk of early recurrence is especially high. The Committee heard from the clinical experts that, on this basis, the use of aromatase inhibitors as primary adjuvant treatment may have maximum benefit among women at highest risk of early recurrence, whereas for women who have a low risk of recurrence the potential for clinical benefit from all hormonal therapy was considered to be much smaller.

4.3.8 Therefore, the Committee considered the notion that for primary adjuvant treatment an aromatase inhibitor might be preferable to tamoxifen on the basis of cost effectiveness in women in whom the risk of early recurrence is particularly high. However, because of the lack of definitive evidence on the relative clinical and cost effectiveness of the use of the aromatase inhibitors in different risk groups, the Committee did not feel able to issue guidance on the relative cost effectiveness of the aromatase inhibitors for the different subgroups. The Committee noted that clarification on the definition of different risk groups, and potentially a consequent variation in treatment strategies, is likely to be reflected in the clinical guideline for early breast cancer currently under development at NICE.

4.3.9 The Committee was aware that the hormone receptors relevant to prognostic and therapeutic decision-making in early breast cancer included both oestrogen receptors and progesterone receptors. The clinical specialists informed the Committee that women who have oestrogen-receptor-negative but progesterone-receptor-positive cancer might also respond well to the use of the aromatase inhibitors. However, the Committee concluded that on the basis of the evidence before it, and the remit from the Department of Health,

the current guidance applies to the group of women with early oestrogen-receptor-positive invasive breast cancer.

- 4.3.10 Finally, the Committee agreed that the choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of the options available. It agreed that consideration of the treatment to be adopted should include whether the woman has received tamoxifen as part of her treatment so far, the licensed indications of the individual drugs, the side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).

[Note: tools will be available when the final guidance is issued]

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit criteria to monitor local practice.

6 Recommendations for further research

6.1 Ongoing clinical trials related to this guidance are:

- a study with more than 6000 participants, comparing 5 years of exemestane with 5 years of anastrozole in preventing cancer recurrence in postmenopausal women who had undergone surgery for primary breast cancer
- a study comparing 5 years of letrozole with 5 years of anastrozole in postmenopausal women with hormone-receptor-positive and lymph-node-positive breast cancer who had undergone recent primary surgery for breast cancer
- a study comparing 5 years of exemestane with 5 years of tamoxifen in postmenopausal women who had undergone surgery to remove early-stage breast cancer; after publication of results from the study of exemestane in unplanned switching, this study was modified to compare 5 years of exemestane with 5 years of tamoxifen crossed over to exemestane
- a study comparing 2 years of exemestane with placebo in women with hormone-receptor-positive breast tumours and very low risk of recurrence.

In addition, the results of the unplanned switching arms from a study discussed in the clinical effectiveness section of this document (comparison of letrozole and tamoxifen) have not been reported yet.

- 6.2 The Committee recommends research into the relative benefit of aromatase inhibitors in different subgroups of women with early breast cancer, stratified by risk of recurrence, and research into the relative cost effectiveness of the different treatment strategies (primary adjuvant, switching and extended adjuvant) that can be used with aromatase inhibitors.

7 Related guidance

- 7.1 NICE has issued the following related clinical guidelines.

- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. *NICE clinical guideline* no. 14 (2004). Available from: www.nice.org.uk/CG014
- Improving outcomes in breast cancer – manual update. *NICE cancer service guidance* (2002). Available from www.nice.org.uk/csgbcguidance

- 7.2 NICE is in the process of developing the following technology appraisals.

- Trastuzumab as adjuvant therapy for early stage breast cancer (publication expected August 2006).
- Paclitaxel for the adjuvant treatment of early node-positive breast cancer (publication expected September 2006).
- Docetaxel for the adjuvant treatment of early node-positive breast cancer (publication expected September 2006).

- 7.3 NICE is in the process of developing the following clinical guideline.

- Breast cancer: diagnosis and treatment (publication expected July 2008).

8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in June 2009.

David Barnett

Chair, Appraisal Committee

July 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler

Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Tom Aslan

General Practitioner, Stockwell, London

National Institute for Health and Clinical Excellence

Final appraisal determination – Hormonal therapies for the adjuvant treatment of early oestrogen receptor positive breast cancer

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay member

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice,
University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital,
Blackpool

Professor Christopher Eccleston

Director, Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital

National Institute for Health and Clinical Excellence

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Dr Elizabeth Haxby

Lead Clinician in Clinical Risk Management, Royal Brompton Hospital

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson

Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Independent Research Consultant

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Vice Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, and Associate Professor, Department of Primary Care and General Practice, University of Birmingham

Simon Thomas

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

B. NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical advisor and a project manager.

Elisabeth George and Zoe Charles

Technical Leads, NICE project team

Louise Longworth

Technical Advisor, NICE project team

Alana Miller

Project Manager, NICE project team

National Institute for Health and Clinical Excellence

Final appraisal determination – Hormonal therapies for the adjuvant treatment of early oestrogen receptor positive breast cancer

Appendix B. Sources of evidence considered by the Committee

A The Assessment Report for this appraisal was prepared by The School of Health and Related Research (ScHARR):

Hind D, Ward S, De Nigris E, et al. *Hormonal therapies for early breast cancer: systematic review and economic evaluation*, January 2006

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- Astra Zeneca
- Novartis Pharma
- Pfizer

II Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Care
- Breast Cancer Campaign
- Cancerbackup
- Association of Surgeons of Great Britain and Ireland
- British Association of Surgical Oncology
- British Oncology Pharmacy Association (BOPA)
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians' Medical Oncology Joint Special Committee

- Royal Pharmaceutical Society
- Society of Endocrinology
- Department of Health
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- NHS Quality Improvement Scotland
- AstraZeneca
- Institute of Cancer Research
- National Cancer Research Institute
- National Coordinating Centre for Health Technology Assessment
- School of Health and Related Research, Sheffield
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on hormonal therapies for the adjuvant by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mr Derek Crawford, Consultant Surgeon, Llandudno General Hospital – clinical expert nominated by British Association of Surgical Oncology
- Professor Ian Smith, Consultant Medical Oncologist, Royal Marsden NHS Foundation Trust – clinical expert nominated by the Institute of Cancer Research
- Mrs Stephanie Jacobs, Chair, Breast Cancer Care – patient expert nominated by Breast Cancer Care

- Mrs Carolyn Morris – patient expert nominated by Cancer Voices

D The following individual(s) representing the National Collaborating Centre responsible for developing the Institute's clinical guideline on early breast cancer guidelines were invited to attend the ACD meeting as observers and to contribute as advisors to the Committee.

- Dr Adrian Harnett, Consultant in Clinical Oncology, Norfolk and Norwich University Hospital NHS Trust