NICE National Institute for Health and Care Excellence

NICE guidance

Fulvestrant for the treatment of locally advanced or metastatic breast cancer

Technology appraisal guidance
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Your responsibility

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All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Guidance

1.1 Fulvestrant is not recommended, within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy.

1.2 Post-menopausal women currently receiving fulvestrant within its licensed indication as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Fulvestrant (Faslodex, AstraZeneca) is an oestrogen antagonist belonging to a class of agents known as selective oestrogen receptor down-regulators (SERDs). Fulvestrant has a UK marketing authorisation for 'the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen'. The recommended dose is 500 mg (administered as two intramuscular injections of 250 mg) every month, with an additional 500 mg dose given 2 weeks after the initial dose.

2.2 According to the summary of product characteristics, the most common side effects associated with fulvestrant are nausea, vomiting, diarrhoea, venous thromboembolism, anorexia, headache, asthenia, urinary-tract infections, hot flushes, back pain, rash, injection-site reactions and hypersensitivity reactions ('British national formulary' [BNF] edition 61). For full details of side effects and contraindications, see the summary of product characteristics.

2.3 The current NHS list price of fulvestrant is £522.41 for 2 x 5 ml (250 mg) prefilled syringes (excluding VAT; BNF edition 61). The first month of treatment with fulvestrant 500 mg includes an additional loading dose administered 2 weeks after the initial dose, resulting in a cost of £1044.82 for the first month. In subsequent months, the cost of fulvestrant 500 mg is £522.41 per month. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of fulvestrant and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer's submission presented clinical-effectiveness data derived from one phase III trial (CONFIRM), supported by results from two dose-ranging phase II trials (FINDER-1 and FINDER-2). Women were eligible for these three studies if they were postmenopausal and had oestrogen-receptor-positive breast cancer. Their cancer could have relapsed during or within 12 months of completing adjuvant hormone therapy (with an anti-oestrogen or an aromatase inhibitor) for early breast cancer; or it could have progressed on anti-oestrogen or aromatase inhibitor therapy for advanced breast cancer provided that this hormone therapy was started more than 12 months after completion of adjuvant hormone therapy (anti-oestrogen or aromatase inhibitor); or it could have progressed while they were on first-line hormone therapy (anti-oestrogen or aromatase inhibitor) for advanced breast cancer. All three trials excluded patients who had received two or more lines of previous hormone therapy for locally advanced or metastatic breast cancer.

3.2 The CONFIRM trial was an international multicentre double-blind parallel-group randomised controlled trial (RCT) that included 736 patients who had previously received an anti-oestrogen or an aromatase inhibitor for the adjuvant treatment of early breast cancer or as palliative therapy for advanced breast cancer. Patients were randomised on a 1:1 basis to receive either fulvestrant 500 mg or fulvestrant 250 mg. The mean age of the patients was 61 years. The baseline characteristics of the groups in the two arms of the trial were generally comparable, although more patients in the fulvestrant 250 mg arm (102 compared with 69) had received radiotherapy as treatment for advanced disease.

3.3 The primary outcome measure in the CONFIRM study was median time to progression (TTP). Median TTP was statistically significantly longer in the overall mixed population (that is, including both patients who had

previously received an anti-oestrogen and patients who had previously received an aromatase inhibitor) for the fulvestrant 500 mg arm compared with the fulvestrant 250 mg arm (6.5 months compared with 5.5 months; hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.68 to 0.94; p = 0.006). A pre-planned analysis was done for the subgroups of patients last treated with an anti-oestrogen (58%) or an aromatase inhibitor (42%). The median TTPs for the fulvestrant 500 mg and fulvestrant 250 mg arms were 8.6 months and 5.8 months respectively (HR 0.76; 95% CI 0.62 to 0.94; p = 0.013) for the population last treated with an anti-oestrogen, and 5.4 months and 4.1 months respectively for the population last treated with an aromatase inhibitor (HR 0.85; 95% CI 0.67 to 1.08; p = 0.195).

3.4 Secondary outcomes reported in the CONFIRM study included objective response rate, clinical benefit rate and overall survival. The results suggested no statistically significant differences between the fulvestrant 500 mg and 250 mg arms for these outcomes, although the median overall survival was greater in the fulvestrant 500 mg group (25.1 months compared with 22.8 months). Log-rank tests suggested a trend for improved overall survival in the fulvestrant 500 mg group (HR 0.84; 95% CI 0.69 to 1.03; p = 0.091). Overall survival data from the CONFIRM trial were not mature: 51% of patients had died at the time of primary data cut-off for TTP. The manufacturer stated that it plans to re-analyse the overall survival data when 75% of patients have died.

3.5 A total of 2443 adverse events were reported by 483 (66%) of the 735 patients in the safety analysis in the CONFIRM trial. A serious adverse event was reported for 54 patients (7%), including 11 patients (1%) who died. Seventeen patients (2%) discontinued fulvestrant treatment because of an adverse event. There were no notable differences in the incidence of adverse events between treatment groups. The most common adverse events were injection-site pain (11.6%), nausea (9.7%) and bone pain (9.4%).

3.6 The manufacturer also provided health-related quality of life data taken from the CONFIRM study for a total of 145 women who completed the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire at baseline. No significant differences were detected

between the fulvestrant 500 mg and 250 mg study arms.

3.7 The FINDER-1 study was a multicentre parallel-group double-blind phase II RCT conducted in Japan. A total of 143 patients recruited from 40 centres were randomised on a 1:1:1 basis to receive fulvestrant 500 mg, fulvestrant 250 mg or fulvestrant 250 mg with a loading dose. The FINDER-2 study was a multicentre international double-blind phase II RCT conducted in seven European countries and Canada. A total of 144 patients were recruited from 34 centres and randomised on a 1:1:1 basis to receive fulvestrant 500 mg, fulvestrant 250 mg or fulvestrant 250 mg with a loading dose. The primary outcome in the FINDER-1 and FINDER-2 trials was objective response rate, with secondary outcomes including clinical benefit rate and TTP. The findings from these trials were broadly in favour of fulvestrant 500 mg compared with fulvestrant 250 mg.

3.8 The manufacturer conducted a network meta-analysis to compare overall survival and TTP for fulvestrant 500 mg with the comparators listed in the scope. Five RCTs that included three of the other comparators (anastrozole, letrozole and fulvestrant 250 mg) listed in the scope were identified in the systematic literature review, resulting in eight trials being included in the network meta-analysis. Data from the total population in the fulvestrant trials were included, with the FINDER-1 and FINDER-2 trials contributing only to the TTP network meta-analysis. The manufacturer stated that inclusion of the group from the CONFIRM trial who had received an aromatase inhibitor as their last treatment did not alter the results in favour of fulvestrant. The manufacturer did not include exemestane as a comparator in the base-case network meta-analysis because of a lack of any relevant trials in which 70% or more patients had documented hormone-receptor-positive advanced breast cancer in a population who had received an anti-oestrogen. Therefore a secondary scenario analysis, as part of the cost-effectiveness analysis comparing fulvestrant 500 mg with exemestane, was carried out by the manufacturer.

3.9 For the base-case network meta-analysis, data on two outcomes were collected: overall survival and TTP. Data from the eight included trials were pooled and extrapolated. Based on patient-level data from the CONFIRM trial, the Weibull distribution was identified as the best-fitting

distribution to estimate overall survival. Because hazard ratios in the CONFIRM trial were constant over time (the shape parameters were very similar for both treatment groups), the relative treatment effects of the alternative treatments were applied to the baseline treatment (fulvestrant 250 mg) using a pooled hazard ratio for overall survival estimated from the network meta-analysis. For TTP, the log-normal distribution was identified by the manufacturer as the best-fitting distribution for data from the CONFIRM trial because it was inappropriate to assume that hazard ratios were constant over time. A simultaneous extrapolation and network meta-analysis of TTP curves for all comparator treatments were derived from the available RCTs. This was done by relating the TTP Kaplan-Meier curves of each of the comparators directly to the parameters of the log-normal survival curves. A fixed-effects model was used to simultaneously extrapolate Kaplan-Meier curves over time by means of log-normal curves, to synthesise and to indirectly compare the different treatments. The shape and scale parameters for the baseline treatment (fulvestrant 250 mg) were estimated and used as the anchor to obtain estimates for the shape and scale parameters of the other comparators. Pooled TTP curves for each treatment were produced and the corresponding area under the curve was calculated to obtain the mean TTP estimates for each treatment.

3.10 The results of the network meta-analysis presented by the manufacturer suggested that fulvestrant 500 mg was associated with longer overall survival compared with fulvestrant 250 mg, anastrozole and letrozole, but this finding was not statistically significant. The results of the TTP network meta-analysis suggested that fulvestrant 500 mg was associated with a statistically significantly longer TTP than fulvestrant 250 mg, whereas anastrozole was associated with a statistically significantly shorter TTP than fulvestrant 250 mg. There were no statistically significant differences in TTP between letrozole 2.5 mg and fulvestrant 250 mg.

3.11 The manufacturer developed an Excel-based cost–utility model, based on a time-in-state model structure. The model structure is similar to that of a Markov cohort model, with three possible health states: pre-progression, post-progression and death. However, instead of using transition probabilities to determine movement between health states,

the model calculates the proportion of patients in each health state according to the estimated survival functions for TTP and overall survival. All patients are assumed to be in the pre-progression health state at model entry (baseline). The duration of second-line hormonal therapy is assumed to be the same as the amount of time spent in the pre-progression health state. The post-progression health state captures a series of subsequent therapies, including third-line hormonal therapy, up to three sequential lines of chemotherapy, and supportive palliative care. Patients can move to the state of death from either the pre-progression or the post-progression health state, which captures death from any cause. The model uses monthly cycles with a lifetime (13-year) time horizon.

3.12 The results of the base-case network meta-analysis of the clinical effectiveness data on TTP and overall survival were used to populate the economic model. For the base-case analysis, comparator treatments were fulvestrant 250 mg, anastrozole and letrozole. The manufacturer used the overall CONFIRM trial population (that is, a mixed population who had received either an anti-oestrogen or an aromatase inhibitor as their last treatment) in the analysis. The manufacturer reported that it was not feasible to analyse the proportion of patients with grade 3 or grade 4 adverse events because adverse events were not reported consistently across the trials included in the network meta-analysis. However, the manufacturer included serious adverse events in the model because sufficient data were available to conduct a network meta-analysis. The serious adverse event data used in the model included both treatment-related and treatment-independent events, because these were available for all relevant RCTs used to derive the estimates of TTP and overall survival in the base-case analysis.

3.13 Health-related quality of life data based on the FACT-B questionnaire were collected at baseline (pre-progression) from a subgroup of patients in the CONFIRM study. However, the model structure required utility values for the pre-progression and post-progression health states that were not collected in the CONFIRM study. Therefore the manufacturer used published pre-progression and post-progression utility values based on a systematic literature review of utility studies for metastatic or locally advanced breast cancer. The manufacturer considered that the

study by Lloyd et al. (2006) provided the most appropriate utility values. In this study, utility values were taken from a relatively small sample of the general public in the UK using the standard gamble technique. The study provided utility values of 0.72 and 0.44 for the pre-progression and post-progression health states respectively. Death was assigned a utility value of zero. Disutilities associated with treatment-related adverse events were not included in the model.

3.14 Resource use and costs in the economic model included those related to each second-line hormonal treatment used during the pre-progression phase, subsequent treatments during the post-progression phase including third-line hormonal therapy, supportive palliative care and chemotherapy, and treatment-related adverse events. No treatment-related monitoring costs associated with fulvestrant 500 mg or its comparators were included in the model. An overall average cost per monthly cycle of £1084 per patient was applied to each treatment arm for the patients in the post-progression health state. For adverse events, the model assumed that each serious adverse event is associated with an average hospital stay of 5 days at a cost of £321.02 per day, which was then weighted by the proportion of serious adverse events estimated in the network meta-analysis for each hormonal treatment considered in the scope. The model assumed that one-third of patients received fulvestrant in primary care and two-thirds in hospital.

3.15 The manufacturer reported the results from the economic model for the two key clinical outcomes, TTP and overall survival. The mean TTP was 15.0 months for fulvestrant 500 mg compared with 10.8 months for fulvestrant 250 mg, 9.5 months for anastrozole and 9.9 months for letrozole. The mean overall survival was 33.4 months for fulvestrant 500 mg compared with 29.0 months for fulvestrant 250 mg, 28.5 months for anastrozole and 24.9 months for letrozole.

3.16 In the base-case incremental analysis, fulvestrant 500 mg was associated with the highest total quality-adjusted life years (QALYs) (1.487 QALYs), followed by fulvestrant 250 mg (1.256 QALYs), anastrozole (1.214 QALYs) and letrozole (1.105 QALYs). Based on an incremental analysis ranking of treatments, the base-case results demonstrated that anastrozole and fulvestrant 250 mg were extendedly

dominated by (that is, were more expensive and less effective than) a combination of two other single-agent treatments, fulvestrant 500 mg and letrozole. The comparison of fulvestrant 500 mg with letrozole produced an incremental cost-effectiveness ratio (ICER) of £31,982 per QALY gained (representing incremental costs of £12,239 and incremental QALYs of 0.383). The manufacturer stated that no patients were assumed to be on an adjuvant switch hormone treatment strategy (that is, sequential treatment with an anti-oestrogen and an aromatase inhibitor).

3.17 The manufacturer conducted deterministic sensitivity analyses by varying key model input parameters. These showed that the key drivers of the cost-effectiveness results were the estimates of TTP and overall survival for all treatments and the utility values assigned to the pre-progression and post-progression health states. The widest range of ICERs was found for the comparison of fulvestrant 500 mg with letrozole, in which the ICERs ranged from £21,894 to £55,160 per QALY gained when the upper and lower 95% credibility limits for the scale and log shape of the log-normal distribution of TTP for letrozole were used.

3.18 The manufacturer also conducted six scenario analyses to assess the impact of key assumptions made in the base-case analysis. These scenarios included: expanding the patient population to allow the inclusion of exemestane in the network meta-analysis (by including trials in which at least 50% of patients had documented hormone-receptor-positive cancer and patients who had last been treated with an aromatase inhibitor [because there are no studies comparing fulvestrant with exemestane in patients treated with an anti-oestrogen]); using alternative proportions for the administration of fulvestrant in the primary care setting and in hospital; altering the cost of the post-progression health state by using an alternative mix of chemotherapies; altering the cost of the post-progression health state by eliminating treatment skipping (patients skip further hormonal treatment if the extent and duration of response to a previous hormonal treatment was insufficient); discounting costs and benefits at 0% and 6%; and altering the time horizon. In summary, exemestane, anastrozole and fulvestrant 250 mg were all extendedly dominated by a combination of fulvestrant 500 mg and letrozole. The comparison of fulvestrant 500 mg with letrozole gave

a range of ICERs from £29,881 to £38,566 per QALY gained.

3.19 The results of the manufacturer's probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY gained, there is a 2% probability of fulvestrant 500 mg being cost effective. This increased to 20% at a threshold of £30,000 per QALY gained.

ERG comments on the manufacturer's submission

3.20 The ERG commented that the manufacturer's systematic review of clinical-effectiveness studies was methodologically appropriate and that all relevant studies meeting the inclusion criteria appeared to have been identified.

3.21 The ERG commented that the CONFIRM study was well designed and that the clinical outcomes reported in this RCT and the supporting phase II trials (FINDER-1 and FINDER-2) address all the relevant outcomes outlined in the scope. However, the ERG noted that fulvestrant is currently most commonly used in clinical practice in England and Wales after aromatase inhibitors and often after an anti-oestrogen as well, and therefore it is a third- or fourth-line hormonal therapy in the treatment pathway for advanced breast cancer. In the fulvestrant trials used as the basis for direct clinical evidence and in the manufacturer's submission, fulvestrant was used in the treatment pathway in the position currently occupied by aromatase inhibitors, as second-line treatment. Therefore, the ERG commented that the generalisability of the patient population and trial results to clinical practice may be questionable, because there is a difference between the indication in the marketing authorisation for fulvestrant and its use in treatment in England and Wales.The ERG also noted that no patients were recruited to CONFIRM from the UK.

3.22 The ERG highlighted that the marketing authorisation for fulvestrant 500 mg specifies that the patient has received previous anti-oestrogen therapy, although the ERG noted that it is not clear from the wording of the marketing authorisation that eligibility for treatment depends on the last therapy received. Therefore, the ERG requested that the manufacturer divide the TTP data from CONFIRM in two main ways. First, the patients were divided into two treatment groups: patients who had

received an anti-oestrogen as their last treatment (58%) and patients who had received an aromatase inhibitor as their last treatment (42%). Second, the patients were split into three treatment groups: patients who had received an anti-oestrogen but not an aromatase inhibitor; patients who had received an aromatase inhibitor but not an anti-oestrogen; and patients who had received both an anti-oestrogen and an aromatase inhibitor. The second set of data was provided 'in confidence'. The ERG noted from the patients divided into two treatment groups that 65.5% of patients who had received an anti-oestrogen as their last treatment were receiving fulvestrant as a first-line treatment for locally advanced or metastatic breast cancer, whereas 66.8% of patients who had received an aromatase inhibitor as their last treatment received fulvestrant as a second-line therapy for advanced breast cancer. The ERG also demonstrated significant differences between the demography of these two groups: the proportion of patients treated with hormone therapy for advanced disease was 34% in the anti-oestrogen group compared with 67% in the aromatase inhibitor group; and the proportion who had received two previous hormone therapies was 4% in the anti-oestrogen group compared with 27% in the aromatase inhibitor group. The ERG therefore speculated that the apparent increased benefit for fulvestrant after an anti-oestrogen rather than after an aromatase inhibitor may be influenced by where in the treatment sequence most patients received fulvestrant, rather than by whether the last treatment before fulvestrant was an anti-oestrogen or an aromatase inhibitor.

3.23 The ERG considered that the manufacturer's base-case economic evaluation was well conducted and closely matched the NICE reference case. The main issue raised by the ERG related to the use of data from the network meta-analysis, which included patients from the CONFIRM trial who had been treated previously with an aromatase inhibitor. The ERG considered it more appropriate to base the model only on patients who had previously received anti-oestrogen therapy, particularly in view of the heterogeneity of the anti-oestrogen and aromatase inhibitor groups. The ERG considered that the advantage of this approach of reducing the heterogeneity of the compared populations outweighed the main disadvantage of reducing the statistical power of the CONFIRM trial.

3.24 In its critique of the network meta-analysis, the ERG noted that in the comparator treatment trials, none of the patients had received a prior aromatase inhibitor. In addition, the ERG noted key differences in the baseline characteristics of the populations in the trials included in the network meta-analysis. For example, the percentage of patients whose oestrogen receptor status was not known to be positive ranged from to 0% (CONFIRM, FINDER-1 and FINDER-2) to 33.1% (Buzdar 1996/98); the proportion of patients treated previously with chemotherapy ranged from 35.1% (Buzdar 1996/98) to 72.5% (FINDER-1); and the proportion of patients with visceral spread was variable, although the ERG noted that the proportion of patients with known visceral spread was high in the fulvestrant trials.

3.25 Overall, the ERG considered that the population in the CONFIRM trial was heterogeneous and that it was not meaningful to regard the group who had received an anti-oestrogen and the group who had received an aromatase inhibitor as similar. The ERG suggested that the network meta-analyses should include data only from patients who had received an anti-oestrogen as their last treatment from the CONFIRM, FINDER-1 and FINDER-2 trials. Therefore the ERG re-ran the analysis using only data from CONFIRM trial patients whose previous hormone therapy was an anti-oestrogen (n = 423). The results were comparable with those obtained when the whole population of the CONFIRM trial was included in the analysis. All hazard ratios for overall survival still favoured fulvestrant 500 mg over other treatments considered in the scope, although the results were not statistically significant.

3.26 For the TTP network meta-analysis, the ERG questioned the assumption that the CONFIRM trial results follow a log-normal distribution. A direct comparison of the Kaplan-Meier analysis of the trial results with the outputs of the manufacturer's log-normal model appeared to suggest a reasonable match between data (TTP) and model. However, the ERG noted some divergence after 18 months, which would affect the projection of survival curves beyond the observed data. Therefore, the ERG argued that because the log-normal parametric model used by the manufacturer did not adequately represent the data on which it was calibrated, it should not be used to calibrate TTP estimates for all comparators included in the network meta-analysis. The ERG observed

that the results of the Kaplan-Meier analysis from the CONFIRM trial showed a higher number of progression events occurring around 90 days, followed by a 90-day period with relatively few new events. From 180 days onward, there was a clear indication of a linear relationship between time and the cumulative TTP hazard. Therefore the ERG proposed that a more accurate approach would be to split the estimation of TTP into two phases and to include only the anti-oestrogen-treated population from the CONFIRM trial. For the first part of the analysis (0–180 days), the ERG performed a network meta-analysis on the log-hazard ratios at 180 days. For the second part of the analysis (after 180 days), TTP was modelled using an exponential distribution, which has a constant hazard or linear cumulative hazard, based on a clear indication of a linear relationship between time and cumulative TTP hazard in the CONFIRM trial. The results of this analysis showed no statistically significant differences in TTP between the groups receiving fulvestrant 500 mg and those receiving other treatments for the first 180 days (a period thought to be driven by protocol activities and short-term events). However, after 180 days (the ERG stated that this period relates to long-term patient experience) fulvestrant 500 mg was associated with statistically significant improvements in TTP compared with anastrozole and letrozole.

3.27 For the overall survival network meta-analysis, the ERG commented that the parametric model used by the manufacturer to estimate overall survival in the network meta-analysis appeared to be a reasonable match with the available CONFIRM trial data. However, the ERG also noted that projections of overall survival beyond the period of observation may be substantially over- or under-estimated because of the complex changes in risk that are likely to apply at later times. Therefore, the ERG suggested that an alternative approach to projective modelling was to consider modelling post-progression patient experience directly on the basis of the trial data, and then to combine pre- and post-progression estimates to obtain the best estimate of overall survival. Examination of post-progression survival data by the ERG showed no statistically significant differences between fulvestrant 500 mg and fulvestrant 250 mg, suggesting that any overall survival gains associated with fulvestrant 500 mg were obtained only in the pre-progression phase (TTP). Therefore the ERG estimated a compatible set of survival

estimates (TTP), post-progression survival and overall survival) for fulvestrant 250 mg, anastrozole and letrozole by calibrating a hazard ratio applied to the overall survival estimated for the fulvestrant 500 mg group, which generated a gain in overall survival equal to the corresponding gain in TTP. The ERG noted that although this is an approximation, it allows the timing of post-progression survival to be calculated without elaborate additional modelling. This approach appeared fully justified for anastrozole, because key clinical trials comparing anastrozole with fulvestrant 250 mg showed no statistically significant differences in TTP or overall survival. However, this approach was less clearly supported in the case of letrozole, because there are no trials that directly compare letrozole with fulvestrant.

3.28 The ERG noted several criticisms about the design of the manufacturer's economic model, which was based on separate parametric models of the time from randomisation to TTP and overall survival. The ERG commented that when different probability distributions are used to represent the two sets of data, or when the same function is used for both but does not satisfy proportional hazards criteria (that is, the risk of an event occurring on one treatment relative to another treatment is assumed not to change over time), it is possible for projected estimates of TTP to exceed the corresponding estimates of overall survival. Although the model corrected any negative post-progression survival estimates to zero, it did not compensate for any resulting overestimation of survival. Overall, the ERG concluded that the design of the manufacturer's economic model is unlikely to provide a robust basis for projecting survival beyond the observed data.

3.29 The ERG identified four issues in relation to the cost data used in the manufacturer's model. First, the manufacturer's model does not account for wastage of part-used dispensed packs at the time of disease progression. Second, the ERG questioned the use of the two expert opinions for pre-progression and post-progression health state costs, and instead proposed that such costs should be based on treatment pathways described in 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81). Third, the manufacturer's model limits drug-related adverse events to serious adverse events only. Fourth, the manufacturer's approach of applying a single average cost

for UK hospital admission is simplistic and inappropriate for costing adverse events associated with treatment complications in advanced breast cancer. The ERG calculated an alternative estimate of £3147 per admission, compared with the estimate in the manufacturer's model of £1605 per episode. Overall, the ERG stated that making these four modifications to the model increased the ICER in all cases but, because each change represents only a small element of the total cost, the increases were small.

3.30 Finally, the ERG noted an error in the utility values assigned to the pre-progression and post-progression health states in the manufacturer's economic model. Utility values were based on the age of the participants in the study by Lloyd et al. (2006), taken from a sample of the general UK population, and not on the age of breast cancer patients. The ERG proposed that, to ensure consistency with standard UK EQ-5D tariff scores, the mean age should be set to 47 years (the mean age of the original UK York study sample used). The ERG also accounted for the 'responder status' of patients (that is, whether or not their cancer responded to treatment) when estimating new utility values for both health states. In summary, using ERG estimated utility values of 0.7733 for the pre-progression state and 0.4964 for the post-progression state reduced the ICER for fulvestrant by £2700 per QALY gained compared with letrozole.

3.31 The ERG made eight separate modifications to explore the impact of the various issues described in the critique of the manufacturer's economic model. Seven modifications were made to the economic model logic or parameter values, and the eighth modification involved using effectiveness data from the anti-oestrogen subgroup in the CONFIRM trial instead of data from the whole trial population. The ERG presented detailed deterministic results separately for the manufacturer's base-case scenario using the whole CONFIRM population and for the anti-oestrogen subgroup.

3.32 In summary, based on the full CONFIRM trial population, the calculated deterministic cost-effectiveness results of the ERG's exploratory analyses showed that fulvestrant 250 mg was extendedly dominated by the other comparators,. The ICERs for anastrozole compared with

letrozole and for fulvestrant 500 mg compared with anastrozole were both close to £30,000 per QALY gained. The ERG's preferred exploratory deterministic cost-effectiveness analysis based on the anti-oestrogen subgroup from CONFIRM and an updated network meta-analysis resulted in fulvestrant 250 mg being extendedly dominated by the other comparators. The ICER for anastrozole compared with letrozole was £1162 per QALY gained, and the ICER for fulvestrant 500 mg compared with anastrozole was £34,972 per QALY gained.

3.33 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TA239

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of fulvestrant, having considered evidence on the nature of locally advanced or metastatic breast cancer and the value placed on the benefits of fulvestrant by women with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the views of the patient experts on their experience of fulvestrant as a treatment for locally advanced or metastatic breast cancer. It heard from one patient expert who is currently receiving fulvestrant and understood that patients value the availability of a further treatment option after aromatase inhibitors and anti-oestrogen therapies, both as a treatment and because it delays the need for chemotherapy. The Committee also heard from this patient expert that she found the disadvantages of having two injections and the associated side effects of fulvestrant were outweighed by the benefits of remaining fit and well on this therapy. The Committee recognised the importance of additional treatment options for post-menopausal women with locally advanced or metastatic breast cancer.

4.3 The Committee considered the licensed indication for fulvestrant. It noted that fulvestrant has a marketing authorisation 'for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen'. The Committee noted comments from the ERG that it is not clear from the wording of the marketing authorisation that eligibility for treatment depends on the last therapy received and may include women who have received more than one previous line of treatment for metastatic breast cancer. However, the manufacturer confirmed that fulvestrant has a marketing authorisation as a second-line treatment for metastatic breast cancer in postmenopausal women after adjuvant or first-line treatment of advanced disease with an anti-oestrogen therapy (for most patients this is usually tamoxifen). The Committee was aware that 42% of the patients in the CONFIRM trial had received an aromatase

inhibitor as their last treatment before fulvestrant. It also heard from the manufacturer that the European Medicines Agency had regarded the results for the group that had received an aromatase inhibitor as being inconclusive and had rejected the manufacturer's request for an extension of the marketing authorisation for fulvestrant to include patients who have experienced treatment failure with an aromatase inhibitor. Therefore the Committee was aware of the restriction of the marketing authorisation to patients who had been treated previously with an anti-oestrogen, and the manufacturer's confirmation about the marketing authorisation, which places fulvestrant, within its licensed indication, as an alternative to aromatase inhibitors after anti-oestrogen treatment.

4.4 The Committee considered the likely position of fulvestrant in the treatment pathway for women with oestrogen-receptor-positive advanced breast cancer in the UK. The Committee also examined the recommendations on the use of hormone therapy in the NICE clinical guidelines 'Early and locally advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 80) and 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81). It observed that aromatase inhibitors were recommended either as the sole, or as a significant part of, adjuvant treatment for most postmenopausal women with oestrogen-receptor-positive early breast cancer. The Committee also understood that aromatase inhibitors were recommended for postmenopausal women with oestrogen-receptor-positive advanced breast cancer who had no history of hormone therapy or who had been treated previously with tamoxifen. It heard from the clinical specialist that clinical practice follows these guidelines, in that most postmenopausal women receive an aromatase inhibitor as adjuvant hormone therapy for early breast cancer or as first-line treatment if presenting with advanced breast cancer. The Committee understood that the use of tamoxifen in clinical practice in postmenopausal women as a sole adjuvant treatment or as a first-line treatment for new locally advanced or metastatic breast cancer is diminishing, apart from in a small group of women with early breast cancer who have a very poor prognosis and in the small proportion of women who are unable to tolerate any aromatase inhibitor. The manufacturer stated in its submission that the split is approximately 20:80 between treatment with aromatase inhibitors and treatment with

anti-oestrogens for patients whose disease progresses on or after adjuvant therapy. However, the Committee heard from the clinical specialist that the proportion of patients receiving aromatase inhibitors is increasing because of changes in clinical practice and therefore aromatase inhibitors are now increasingly favoured over anti-oestrogens. The clinical specialist also indicated that there was not thought to be any significant clinical difference between the effectiveness of anastrozole and letrozole for treating advanced disease. The clinical specialist informed the Committee that exemestane or tamoxifen may be offered as a second-line treatment to women whose disease has failed to respond to an aromatase inhibitor given as either adjuvant therapy or first-line treatment for advanced disease, with the choice depending on a variety of factors, including an assessment of how well previous treatment had worked. The Committee heard from the clinical specialist that fulvestrant is currently considered to be a third-line or fourth-line treatment for postmenopausal women with metastatic breast cancer in UK clinical practice. It further heard that there is little or no clinical evidence about the optimal treatment sequence for advanced breast cancer beyond first-line treatment. The Committee considered that the most likely position of fulvestrant in UK clinical practice would remain as a third-line or fourth-line treatment after therapy with aromatase inhibitors and/or an anti-oestrogen therapy. The Committee again noted the difference between the manufacturer's submission and clinical practice, and that fulvestrant was restricted by its marketing authorisation to use after treatment with an anti-oestrogen. However, based on the manufacturer's confirmation about the marketing authorisation for fulvestrant (see section 4.3), the Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal.

4.5 The Committee considered the relevant comparator treatments for fulvestrant within its licensed indication. It understood that the scope listed low-dose (250 mg) fulvestrant and aromatase inhibitors (anastrozole, exemestane and letrozole) as the relevant treatment comparators. It heard from the manufacturer that fulvestrant 250 mg has been replaced by fulvestrant 500 mg as the licensed dose. The Committee considered the remaining comparators. It noted that for the only positions in the treatment pathway for which evidence for

fulvestrant was available, non-steroidal aromatase inhibitors such as anastrozole and letrozole are the most likely treatments to be used in clinical practice. It heard from the clinical specialist that, for women who are unable to tolerate non-steroidal aromatase inhibitors, exemestane would be the appropriate comparator if they have been treated previously with an anti-oestrogen. The Committee concluded that the aromatase inhibitors anastrozole, letrozole and exemestane are the most appropriate comparators for the appraisal of fulvestrant.

Clinical effectiveness

4.6 The Committee considered the clinical-effectiveness data from the CONFIRM trial. It noted that the only comparator in CONFIRM was low-dose (250 mg) fulvestrant. Relative to this comparator, the Committee noted that fulvestrant 500 mg offered benefits in increasing the TTP, but that the difference between groups was statistically significant only for those patients whose last therapy was an anti-oestrogen, and not for patients whose last therapy was an aromatase inhibitor. However, the Committee was also aware that the CONFIRM trial was not powered to detect a statistically significant difference in TTP between fulvestrant 500 mg and fulvestrant 250 mg in the two patient subgroups. The Committee concluded that fulvestrant 500 mg offered some clinical benefit compared with fulvestrant 250 mg.

4.7 The Committee noted that the results of the network meta-analyses by the manufacturer showed no statistically significant differences in overall survival between fulvestrant, anastrozole and letrozole, although fulvestrant resulted in statistically significantly longer TTP compared with anastrozole (but not letrozole). In addition, the Committee observed that parametric survival models had been used to estimate TTP (log-normal distribution) and overall survival (Weibull distribution) for fulvestrant and other comparators included in the network meta-analysis. The Committee agreed with the issues identified by the ERG about the fit of the log-normal survival model used by the manufacturer to estimate TTP for fulvestrant and other comparators included in the network. It agreed that this resulted in a small number of patients with very long TTPs, which was likely to significantly influence the mean TTP. The Committee also noted that, although the parametric model the manufacturer used to

estimate overall survival in the network meta-analysis appeared to be a reasonable match with the CONFIRM trial data, the projections of overall survival beyond the period of observation may have been substantially over- or under-estimated because of the complex changes in risk that were likely to apply at later times. Therefore, the Committee concluded that there was high uncertainty about the validity of the results of the network meta-analyses used to estimate TTP and overall survival.

4.8 The Committee considered the populations of the trials included in the network meta-analysis, which included aromatase inhibitors as comparators. It was aware that, although the marketing authorisation for fulvestrant 500 mg is for patients who have received previous anti-oestrogen treatment, the CONFIRM, FINDER-1 and FINDER-2 trial populations included some patients who had last received an aromatase inhibitor, whereas all other trials in the network included only patients who had previously received an anti-oestrogen. The Committee further noted differences in the previous anti-oestrogen and previous aromatase inhibitor groups relating to the position of fulvestrant as a first-line or second-line therapy. Data from CONFIRM showed that most (65.5%) patients receiving fulvestrant after an anti-oestrogen therapy received fulvestrant as a first-line treatment for metastatic breast cancer and the remainder (34.5%) received fulvestrant as a second-line treatment for metastatic breast cancer. Conversely, of the patients who received an aromatase inhibitor as their last treatment before fulvestrant, most (66.8%) received fulvestrant as a second-line treatment for advanced breast cancer. The Committee also noted the differences in demography in the anti-oestrogen and aromatase inhibitor populations and agreed with the ERG that these two groups were heterogeneous. Therefore the Committee agreed that only data from the subgroup in the CONFIRM trial who had received an anti-oestrogen as their last treatment before fulvestrant should be included in the network meta-analyses, in line with the marketing authorisation for fulvestrant.

4.9 The Committee considered the eligibility criteria for trials included in the network meta-analysis. It was aware that CONFIRM, FINDER-1 and FINDER-2 were the only trials with an entire patient population documented as having oestrogen-receptor-positive breast cancer. The Committee noted that the manufacturer had sought advice from key

opinion leaders about setting firm criteria for the selection of trials for inclusion in the meta-analysis (for example, including only recent trials, or agreeing a stipulated percentage of patients with cancer of unknown oestrogen receptor status), but that no such criteria could be agreed. The main inclusion criterion was relaxed by the manufacturer to include trials for comparators with at least 70% of patients with documented oestrogen-receptor-positive status. The Committee was aware that, based on this criterion, exemestane was excluded as a comparator because of the lack of any relevant trials with at least 70% of patients with oestrogen-receptor-positive cancer. The Committee noted that the percentage of patients with oestrogen-receptor-negative cancer in the trials included in the network meta-analysis ranged from 0% to 33%. The Committee also highlighted sources of heterogeneity between the trials included in the network meta-analysis, including inclusion criteria, median duration of follow-up, amount of previous chemotherapy given, types of recurrent and metastatic disease and the wide timespan of the included trials, which were published between 1996 and 2010. The Committee noted that fulvestrant 500 mg was linked to other treatments in the network only through fulvestrant 250 mg, which was used as the baseline comparator in the manufacturer's network meta-analysis. The Committee further noted that the baseline characteristics of the patients enrolled in the CONFIRM, FINDER-1 and FINDER-2 trials may not be directly comparable with those of patients enrolled in earlier studies that compared fulvestrant 250 mg with anastrozole. The Committee also observed that the results of the network meta-analyses suggested better outcomes in terms of overall survival and TTP for letrozole 0.5 mg (which does not have a marketing authorisation for this indication) than for letrozole 2.5 mg (which does have a marketing authorisation for this indication) when compared with fulvestrant 500 mg. The Committee noted the results of two other trials (Dombernowsky et al. 1998; Gershanovich et al. 1998) that were excluded from the network meta-analyses (because they did not meet the oestrogen-receptor-positive status inclusion criterion) in which there was a trend suggesting clinical superiority of letrozole 2.5 mg over letrozole 0.5 mg. The Committee concluded that the results of the manufacturer's network meta-analysis were subject to bias from the selection of studies included in the network and this therefore increased the uncertainty about the outputs of this analysis.

4.10 The Committee again discussed the parametric survival models used to project TTP and overall survival by the manufacturer. It accepted the ERG's exploratory analyses that derived the best estimate of overall survival from modelling post-progression on the basis of trial data and combining pre-progression and post-progression estimates. Overall, the Committee concluded that the manufacturer did not provide sufficient commentary or analysis of uncertainty about the fit of alternative parametric survival models and concluded that the estimates of TTP and overall survival based on the ERG's exploratory analysis were more appropriate and were therefore preferred.

Cost effectiveness

4.11 The Committee considered the manufacturer's economic model and the ERG's critique of the model. The Committee agreed with the ERG that because two different probability distributions were fitted to the two sets of data, it is possible for projected estimates of TTP to exceed the corresponding estimates of overall survival, which can lead to negative values for the number of patients alive in the post-progression state in the economic model. The Committee noted that, although the model corrected any negative post-progression survival estimates to zero, it did not compensate for any resulting overestimation of survival. The Committee concluded that the manufacturer's economic model is unlikely to provide a robust basis for projecting survival data beyond the observed data from the CONFIRM trial.

4.12 The Committee discussed the utility values applied to the pre-progression and post-progression health states by the manufacturer. The Committee agreed that, although the utility values (taken from Lloyd et al. 2006) were not generated in line with the NICE reference case, they probably represent the best published estimates available, although methodological uncertainty remains. However, it agreed that the utility values based on the age of the participants in the study by Lloyd et al. (2006) should have been adjusted to the mean age of patients used to estimate UK EQ-5D tariff scores. The Committee also agreed with the ERG that the 'responder status' of patients should have been incorporated in the estimation of utility values for the pre-progression and post-progression health states. The Committee concluded that the

ERG's adjusted utility values used in its exploratory analysis were preferable to those used by the manufacturer.

4.13 The Committee discussed the validity of the cost inputs used in the manufacturer's economic model. The Committee agreed with the ERG in relation to uncertainty about some of the cost inputs used and that modifications to these parameters resulted in small increases in the ICERs. The Committee also noted that the list price of anastrozole reported in the manufacturer's submission may not be what the NHS usually pays. Therefore the Committee concluded that it is likely that the ICERs for fulvestrant compared with anastrozole would be underestimated.

4.14 The Committee noted that the key drivers of the cost-effectiveness results in the manufacturer's model were the estimates of TTP and overall survival for all treatments and the utility values assigned to the pre-progression and post-progression health states. The Committee highlighted the results of the manufacturer's probabilistic sensitivity analysis, which indicated that fulvestrant 500 mg had a low probability of being cost effective (2%) at a threshold of £20,000 per QALY gained. The Committee also considered that the ICERs generated using the manufacturer's model were not reliable because of problems with the design of the model and the inclusion of the mixed patient population from the CONFIRM trial. The Committee agreed that the ICERs generated by the ERG's exploratory analysis – which used different estimates of TTP and overall survival, included only the population from the CONFIRM trial whose last treatment had been an anti-oestrogen, revised cost inputs and adjusted the utility estimates – would be more reliable. However, the Committee noted that the ERG's exploratory analysis was based on the same trials in the network meta-analysis as those used in the manufacturer's network meta-analysis. The Committee considered that the network meta-analysis contained considerable uncertainty, which was unaccounted for in the ICERs. Overall, the Committee concluded that the ERG's ICER of £35,000 per QALY gained for fulvestrant 500 mg compared with anastrozole was more plausible than the manufacturer's base-case estimate but there remained considerable uncertainty about this estimate.

4.15 The Committee noted that no comparison with exemestane could be made in the manufacturer's base-case cost-effectiveness analysis because of a lack of any relevant trials in which 70% or more of patients had oestrogen-receptor-positive advanced breast cancer in a population who had received an anti-oestrogen. The Committee noted that, as a result, the cost effectiveness of fulvestrant compared with exemestane in this patient population remains unknown. The Committee further concluded that a cost-effectiveness analysis for a subgroup of patients with contraindications to non-steroidal aromatase inhibitors would be desirable, but because the comparator treatment in such an analysis would be exemestane, this could not be undertaken. The Committee concluded that it was unable to recommend fulvestrant as an alternative to exemestane in postmenopausal women with oestrogen-receptor-positive, locally advanced or metastatic breast cancer, or disease progression on therapy with an anti-oestrogen who have contraindications to non-steroidal aromatase inhibitors.

4.16 The Committee considered the small subgroup of women who are unable to tolerate treatment with any aromatase inhibitor. The Committee noted that there was no available evidence on the clinical and cost effectiveness of fulvestrant for this small subgroup, and concluded that it was unable to recommend fulvestrant for women unable to tolerate both non-steroidal and steroidal aromatase inhibitors. However, the Committee was aware of alternative funding arrangements available for providing treatment for women who are unable to tolerate an aromatase inhibitor, such as individual funding requests based on exceptionality.

4.17 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all of the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.18 The Committee discussed whether fulvestrant fulfilled the criteria for a life-extending, end-of-life treatment. The Committee agreed that, based on the results of the CONFIRM trial, fulvestrant is indicated for patients with a life expectancy of more than 24 months (the ERG's estimate of mean overall survival for patients taking fulvestrant 500 mg was 36.33 months compared with 32.31 months for those taking anastrozole and 30.90 months for those taking letrozole) and so the criterion of patients with a short life expectancy was not met. Therefore, the Committee agreed that it was not necessary for the criteria of extension to life of at least an additional 3 months and a small patient population to be established. The Committee concluded that fulvestrant did not fulfil the end-of-life criteria.

4.19 The Committee considered the most plausible ICER for fulvestrant compared with anastrozole, which it had agreed was likely to be at least £35,000 per QALY gained (see section 4.14). The Committee also noted the considerable uncertainty associated with this estimate because of the network meta-analysis. The Committee concluded that fulvestrant could not be considered a cost-effective use of NHS resources as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in post-menopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy.

4.20 The Committee considered a potential equalities issue highlighted during consultation about the use of fulvestrant for patients unable to swallow oral aromatase inhibitor medication. The Committee was aware that women who are unable to swallow (for example, following a stroke) would be fed using an enteral tube, and that oral medication can also be given by this route. In addition, given that the recommendation did not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any

specific group compared with other groups.

Summary of Appraisal Committee's key conclusions

TA239	Appraisal title: Fulvestrant for the treatment of locally advanced or metastatic breast cancer	Section
Key conclusion		
Fulvestrant is not recommended, within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy. Reasons for recommendation: • Fulvestrant has a marketing authorisation for patients who have been treated previously with an anti-oestrogen (that is; second line as an alternative to aromatase inhibitors). • The CONFIRM trial population consisted of a mixture of patients who had last received either an anti-oestrogen or an aromatase inhibitor. The only comparator included in the CONFIRM trial was fulvestrant 250 mg. • There was high uncertainty about the validity of the manufacturer's network meta-analysis because of heterogeneity between the studies included, the selection of studies included and the parametric survival models used to project TTP and overall survival. • The most plausible ICER presented for fulvestrant 500 mg compared with anastrozole was £35,000 per QALY gained (based on the ERG's exploratory analysis). However, there remained considerable uncertainty about this estimate because it was based on the same trials in the network meta-analysis as those used in the manufacturer's network meta-analysis. • The Committee concluded that fulvestrant did not fulfil the end-of-life criteria as it is indicated for patients with a life expectancy of more than 24 months.		1.1 4.3, 4.6, 4.7, 4.9, 4.14, 4.18
Current practice		

Clinical need of patients, including the availability of alternative treatments	The Committee heard from the patient expert about the value of having a further treatment option after aromatase inhibitors and anti-oestrogen therapies. The Committee recognised the importance of additional treatment options for post-menopausal women with locally advanced or metastatic breast cancer.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee noted that although fulvestrant 500 mg offered benefits in increasing the TTP compared with low-dose (250 mg) fulvestrant in the CONFIRM trial, this difference was statistically significant only for patients whose last therapy was an anti-oestrogen, and not for patients whose last therapy was an aromatase inhibitor. However, the Committee was also aware that the CONFIRM trial was not powered to detect a statistically significant difference in TTP between fulvestrant 500 mg and fulvestrant 250 mg in the two patient subgroups. The Committee noted that the results of the network meta-analyses by the manufacturer showed no statistically significant differences in overall survival between fulvestrant, anastrozole and letrozole, although fulvestrant resulted in statistically significantly longer TTP compared with anastrozole (but not letrozole). However, the Committee concluded there was high uncertainty about the validity of these results because of the parametric survival models used. No specific claim for innovation was made.	4.6, 4.7

What is the position of the treatment in the pathway of care for the condition?	The manufacturer confirmed that fulvestrant has a marketing authorisation as a second-line treatment for metastatic breast cancer in postmenopausal women after adjuvant or first-line treatment of advanced disease with an anti-oestrogen therapy (for most patients this is usually tamoxifen). The Committee was aware that the marketing authorisation places fulvestrant as an alternative to aromatase inhibitors after anti-oestrogen treatment. The Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal. The Committee concluded that the aromatase inhibitors anastrozole, letrozole and exemestane are the most appropriate comparators for the appraisal of fulvestrant.	4.3, 4.4, 4.5
Adverse effects	The Committee heard from one patient expert who is currently receiving fulvestrant that the disadvantages of having two injections and the associated side effects of fulvestrant were outweighed by the benefits of remaining fit and well on this therapy.	4.2
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The Committee was aware that the only treatment comparator in the CONFIRM trial was low-dose (250 mg) fulvestrant. The Committee noted that although the marketing authorisation for fulvestrant 500 mg is for patients who have received previous anti-oestrogen treatment, the CONFIRM trial population consisted of a mixture of patients who had last received either an anti-oestrogen or an aromatase inhibitor. The Committee noted heterogeneity between these two subgroups in terms of previous treatment and patient characteristics. The Committee therefore agreed that only data from the subgroup in the CONFIRM trial who had received an anti-oestrogen as their last treatment should be included in the network meta-analyses. The Committee noted that fulvestrant 500 mg was linked to other treatments in the network only through fulvestrant 250 mg, which was used as the baseline comparator in the manufacturer's network meta-analysis. The Committee noted that the manufacturer had sought advice from key opinion leaders about setting firm criteria for the selection of trials for inclusion in the meta-analysis (for example, including only recent trials, or agreeing a certain percentage of patients with cancer of unknown oestrogen receptor status), but that no such criteria could be agreed. The main inclusion criterion was relaxed by the manufacturer to include trials for comparators with at least 70% of patients with documented oestrogen-receptor-positive status. The Committee was aware that, based on this criterion, exemestane was excluded as a comparator in the base-case cost-effectiveness analysis. The Committee also highlighted sources of heterogeneity between the trials included in the network meta-analysis. The Committee concluded that the results of the manufacturer's network meta-analysis were subject to bias from the selection of studies included in the network.	4.6, 4.8, 4.9

Relevance to general clinical practice in the NHS	The Committee was aware of the restriction to the marketing authorisation to patients who had been treated previously with an anti-oestrogen, which places fulvestrant as an alternative to aromatase inhibitors after anti-oestrogen treatment. The Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal.	4.3, 4.4
Uncertainties generated by the evidence	The Committee concluded that there was high uncertainty about the validity of the results of the manufacturer's network meta-analysis because of heterogeneity between the studies selected and the parametric survival models used to project TTP and overall survival.	4.7, 4.9, 4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that the CONFIRM trial population consisted of a mixture of patients who had last received either an anti-oestrogen or an aromatase inhibitor. The Committee noted heterogeneity between these two subgroups in terms of previous treatment and patient characteristics. The Committee therefore agreed that only data from the subgroup in the CONFIRM trial who had received an anti-oestrogen as their last treatment should be included in the network meta-analyses, in line with the marketing authorisation for fulvestrant.	4.8
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that the results of the network meta-analyses by the manufacturer showed no significant differences in overall survival between fulvestrant, anastrozole and letrozole, although fulvestrant resulted in significantly longer TTP compared with anastrozole (but not letrozole). However, the Committee concluded that, because of the issues identified by the ERG concerning the fit of the parametric survival models used by the manufacturer, there was high uncertainty about these results.	4.7
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee agreed with the ERG that because two different probability distributions were fitted to the two sets of data, it is possible for projected estimates of TTP to exceed the corresponding estimates of overall survival, which can lead to negative values for the number of patients alive in the post-progression state in the economic model. The Committee concluded that the manufacturer's economic model is unlikely to provide a robust basis for projecting survival data beyond the observed data from the CONFIRM trial.	4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee discussed the validity of the cost inputs used in the manufacturer's economic model. The Committee agreed with the ERG in relation to the cost data used and that modifications to these parameters resulted in small increases in the ICERs for fulvestrant. The Committee also considered that the ICERs generated using the manufacturer's model were not reliable because of problems with the design of the model and the inclusion of the mixed patient population from the CONFIRM trial.	4.13, 4.14

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee discussed the utility values applied to the pre-progression and post-progression health states by the manufacturer. The Committee agreed that, although the utility values were not generated in line with the NICE reference case, they probably represent the best published estimates available. However, the Committee agreed with the ERG that the utility values should have been adjusted for the age and 'responder status' of the patients. No evidence of additional benefits (other than those already accounted for in the QALY) of treatment with fulvestrant was presented or identified.	4.12

Are there specific groups of people for whom the technology is particularly cost effective?	The Committee noted that no comparison with exemestane could be made in the manufacturer's base-case cost-effectiveness analysis because of a lack of any relevant trials in which 70% or more of patients had oestrogen-receptor-positive advanced breast cancer in a population that had an anti-oestrogen as their last treatment. The Committee noted that, as a result, the cost effectiveness of exemestane compared with fulvestrant in this patient population remains unknown. The Committee thought that a cost-effectiveness analysis for a subgroup of patients with contraindications to non-steroidal aromatase inhibitors would be desirable, but that such an analysis could not be undertaken. The Committee concluded that it was unable to recommend fulvestrant as an alternative to exemestane in postmenopausal women with oestrogen-receptor-positive, locally advanced or metastatic breast cancer, or disease progression on therapy with an anti-oestrogen who are contraindicated to non-steroidal aromatase inhibitors. The Committee also noted that there was no available clinical and cost-effectiveness evidence on fulvestrant for the small subgroup of women who are unable to tolerate treatment with any aromatase inhibitor.	4.15, 4.16
What are the key drivers of cost effectiveness?	The Committee noted that the key drivers of the cost-effectiveness results in the manufacturer's model were the estimates of TTP and overall survival for all treatments and the utility values assigned to the pre-progression and post-progression health states.	4.14

Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the ICERs generated by the ERG's analysis – which used different estimates of TTP and overall survival, included only the population from the CONFIRM trial whose last treatment had been an anti-oestrogen, revised cost inputs and adjusted utility estimates – would be more reliable than the ICERs generated in the manufacturer's model. Therefore, the Committee concluded that the ICER of £35,000 per QALY gained for fulvestrant 500 mg compared with anastrozole was more plausible than the manufacturer's base-case estimate but there remained considerable uncertainty about this estimate.	4.14
Additional factors taken into account		
Patient access schemes (PPRS)	No approved patient access scheme was submitted for the technology being appraised.	
End-of-life considerations	The Committee concluded that fulvestrant did not fulfil the end-of-life criteria because, based on the results of the CONFIRM trial, fulvestrant is indicated for patients with a life expectancy of more than 24 months.	4.18
Equalities considerations and social value judgements	The Committee considered a potential equalities issue highlighted during consultation about the use of fulvestrant for patients unable to swallow oral aromatase inhibitor medication. The Committee was aware that women who are unable to swallow (for example, following a stroke) would be fed using an enteral tube, and that oral medication can also be given by this route. In addition, given that the recommendation did not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups.	4.20

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website.

- A costing statement explaining the resource impact of this guidance.

6 Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009).
- Early and locally advanced breast cancer: diagnosis and treatment. NICE clinical guideline 80 (2009).
- Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal guidance 116 (2007).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk)

- Eribulin for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance (publication date to be confirmed).

7 Review of guidance

7.1 The guidance on this technology will be considered for review in August 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
December 2011

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor Usha Chakravarthy
Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon
Senior Lecturer in Health Economics, University of Sheffield

Dr Martin Duerden
Assistant Medical Director, Betsi Cadwaladr University Health Board

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Gillian Ells
Prescribing Adviser, NHS Sussex Downs and Weald

Dr Jon Fear
Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh
Senior Lecturer and Honorary Consultant, University of Liverpool

Niru Goenka
Consultant Physician, Countess of Chester NHS Foundation Trust

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Alison Hawdale
Lay member

Professor John Hutton
Professor of Health Economics, University of York

Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Dr Steven Julious
Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Rachel Lewis
Advanced Nurse Practitioner, Manchester Business School

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Professor Femi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge
GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray D Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Cliff Snelling
Lay member

Charles Waddicor
Chief Executive, NHS Berkshire

Mike Wallace
Health Economics and Reimbursement Director, Johnson & Johnson Medical Ltd

Dr Lok Yap
Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

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 adviser and a project manager.

Matthew Dyer
Technical Lead

Joanne Holden
Technical Adviser

Kate Moore
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Fleeman N, Bagust A, Boland A et al. Fulvestrant for the treatment of locally advanced or metastatic breast cancer: a single technology appraisal (June 2011)

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- AstraZeneca

II Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- Macmillan Cancer Support
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety, Northern Ireland
- Healthcare Improvement Scotland
- AstraZeneca
- Pfizer
- Liverpool Reviews and Implementation Group
- National Institute for Health Research Technology Assessment Programme

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on fulvestrant by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Andreas Makris, Consultant Clinical Oncologist, nominated by Royal College of Physicians – clinical specialist
- Tara Beaumont, Clinical Nurse Specialist, nominated by Breast Cancer Care – patient expert
- Marie Hecht, nominated by Breast Cancer Care – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AstraZeneca

Changes after publication

March 2014: minor maintenance

June 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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