

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Pre-meeting briefing

Fulvestrant for the treatment of locally advanced or metastatic breast cancer

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- a version of the clinical study report and a copy of the protocol and statistical analysis plan for the pivotal clinical trial (CONFIRM)
- information on the length of follow-up and treatment duration for each study arm in the CONFIRM trial
- further information on previous adjuvant therapy and previous advanced disease therapies for each study arm in the CONFIRM trial
- any additional mature survival data from the CONFIRM trial
- information on the post-progression treatments given to patients in both arms of the CONFIRM trial
- further information on the conduct of the network meta-analyses and relevant data used in the analyses
- product-limit survival tables from analysis of CONFIRM trial data
- copies of all documents cited in the reference list, in electronic format

Licensed indication

Fulvestrant (Faslodex, AstraZeneca) 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'.

Key issues for consideration

Clinical effectiveness

- The licensed indication potentially permits the use of fulvestrant as:
 - a first-line metastatic treatment for women who have received prior anti-oestrogen therapy for early breast cancer
 - a second-line metastatic treatment for women who have received prior anti-oestrogen therapy for metastatic breast cancer
 - a third- or fourth-line metastatic treatment for women whose prior treatment was an anti-oestrogen, but who may have had one or more aromatase inhibitor therapies prior to an anti-oestrogen.
- A submission by the manufacturer to the EMA Committee for Medicinal Products for Human Use (CHMP) to extend the indication of fulvestrant to include patients who had failed on aromatase inhibitors was rejected.
- The CONFIRM trial includes a mixed, heterogeneous patient population whose previous therapy was *either* an anti-oestrogen or an aromatase inhibitor.
- The CONFIRM trial excludes:
 - women who had received two or more lines of previous endocrine therapy for locally advanced or metastatic breast cancer
 - women who have life-threatening metastatic visceral disease.
- Two thirds of the CONFIRM population received fulvestrant as a first-line treatment for locally advanced or metastatic breast cancer.
- CONFIRM compares fulvestrant 500 mg with fulvestrant 250 mg. The evidence comparing fulvestrant with comparators in the NICE scope comes from a network meta-analysis in which:
 - none of the other trials included patients who had received a prior aromatase inhibitor
 - the percentage of patients with unknown oestrogen receptor status varied between the other trials
 - the percentage of patients receiving prior chemotherapy varied between the trials

- the time to relapse before commencing fulvestrant (or other second-line therapy) was unknown
- the estimated hazard ratio (HR) of overall survival (OS) (that is, the risk of death) was 1.20 with letrozole and 1.02 with anastrozole
- the ERG consider the results to be unreliable.
- It was not possible to compare fulvestrant 500 mg with exemestane following anti-oestrogen therapy.
- No comparative data for adverse events (AEs) were available.

Cost effectiveness

- Appropriateness of the results of the network meta-analysis for estimating overall survival and time-to-progression in the economic model (CONFIRM population or post anti-oestrogen only population) and the robustness of the parametric models used to project the available pivotal clinical trial data for the remainder of patients' lifetimes.
- Appropriateness of the utility values assigned to the pre- and post-progression health states in the economic model.

1 Decision problem

1.1 *Decision problem approach in the manufacturer's submission*

Population	Postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer, whose disease has progressed or relapsed while on or after endocrine (anti-oestrogen) therapy	As per scope; however, a secondary analysis was presented where clinical data are available for exemestane in which the population includes patients who have received either an anti-oestrogen or an aromatase inhibitor
Intervention	Fulvestrant at its licensed dose of 500 mg	As per scope
Comparators	Low-dose (250 mg) fulvestrant, aromatase inhibitors (anastrozole, exemestane and letrozole)	As per scope. However, based on the licensed population for fulvestrant 500 mg, no clinical data are available for exemestane in the base case analysis. Therefore, a secondary analysis is presented where clinical data are available for exemestane
Outcomes	Overall survival, progression-free survival, response rate, adverse effects, health-related quality of life	As per scope. However, response rates were not considered clinically relevant to include in the model by the manufacturer
Economic evaluation	Cost–utility analysis from an NHS and personal social services (PSS) perspective	As per scope. Lifetime time horizon (13 years)

1.2 *Evidence Review Group comments*

1.2.1 Population

The ERG stated that the patient population described in the decision problem accurately reflects the population for whom the EU licence for fulvestrant 500 mg applies. However, the ERG commented that the patient population addressed in the pivotal CONFIRM trial is broader and includes patients who failed previous endocrine therapy, which may have been an anti-oestrogen or an aromatase inhibitor. The ERG commented that the post-anti-oestrogen and

post-aromatase inhibitor patients should be treated separately because the post-aromatase inhibitor population is not a European Medicines Agency (EMA) licensed population.

1.2.2 Intervention

The ERG considered that the description of the intervention in the decision problem is appropriate.

1.2.3 Comparators

In the CONFIRM trial, fulvestrant 500 mg was compared with fulvestrant 250 mg; aromatase inhibitors were included as comparators in the network meta-analyses and economic evaluation. The ERG commented that aromatase inhibitors are the most appropriate comparators for fulvestrant 500 mg because they are the most frequently used endocrine therapies for locally advanced or metastatic breast cancer. However, the ERG also acknowledged that, even using indirect evidence, it is not possible to compare fulvestrant 500 mg with exemestane in a post-anti-oestrogen population due to absence of trial data in this patient population.

1.2.4 Outcomes

The ERG stated that the outcomes included in the decision problem are appropriate. The ERG noted that the manufacturer's definition of time to progression (TTP) includes disease progression or death, which is more commonly known as progression-free survival.

1.2.5 Timeframe

The ERG noted that the mean duration of treatment in the CONFIRM trial was 10.4 months in the fulvestrant 500 mg group, which differed from the mean duration of treatment of 14 months derived from the network meta-analysis.

1.3 Statements from professional/patient groups and nominated experts

NICE received statements from Breast Cancer Care, the Royal College of Pathologists and a joint statement from the National Cancer Research Institute/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Council for Clinical Oncology (NCRI/RCP/RCR/ACP/JCCO).

Alternative therapies to fulvestrant include anastrozole and letrozole (non-steroidal aromatase inhibitors) and exemestane (steroidal aromatase inhibitor) as well as tamoxifen (anti-oestrogen) and progestogens such as megestrol acetate. A further alternative is chemotherapy.

The clinical specialists commented that letrozole and anastrozole are commonly used as first-line endocrine therapies, followed by the steroidal aromatase inhibitor exemestane for oestrogen receptor positive locally advanced or metastatic breast cancer. Tamoxifen is used less than in previous years and is sometimes used as adjuvant therapy or as second- or third-line treatment. Optimal sequencing of endocrine therapies has not been defined and there is some variation in current practice. There is also some variation as to at what stage chemotherapy is used rather than second-, third- or fourth-line endocrine therapy. The clinical specialists stated that the main advantages of other endocrine therapies over fulvestrant are that they are orally administered and cheaper.

Fulvestrant treatment is initiated by a consultant oncologist or surgeon and then administered on a monthly basis via deep intramuscular injection by a trained nurse either in hospital or a primary care setting. The patient groups commented that current treatment with fulvestrant requires travel to hospital outpatient clinics, which imposes an additional financial burden on patients. The clinical specialists stated that no subgroups will be put at risk by fulvestrant; although patients with blood clotting abnormalities may experience large haematomas, this can be avoided by a simple blood test prior to

treatment. It was also noted by the specialists and patient groups that patients do not find the administration of fulvestrant particularly troublesome and that it ensures higher compliance rates compared with oral aromatase inhibitors. The implementation and delivery of this treatment is unlikely to require any additional NHS resources such as extra training or equipment.

2 Clinical effectiveness evidence

2.1 *Clinical effectiveness in the manufacturer's submission*

The key evidence for the clinical effectiveness of fulvestrant is derived from one phase III trial (CONFIRM), supported by results from two dose-ranging phase II trials (FINDER-1 and FINDER-2). All three trials excluded patients who had received two or more lines of previous endocrine therapy for locally advanced or metastatic breast cancer.

2.1.1 CONFIRM trial

The CONFIRM trial was an international, multi-centre, double-blind, parallel-group randomised controlled trial (RCT) that included 736 patients who had previously received an anti-oestrogen or aromatase inhibitor for adjuvant treatment of early or 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 study participants was 61 years. The baseline characteristics for both arms of the trial were generally comparable, although more patients in the fulvestrant 250 mg arm (102 vs. 69) had received radiotherapy as treatment for advanced disease.

The primary outcome measure used in the CONFIRM study was median TTP. Median TTP was statistically significantly longer in the overall mixed population for the fulvestrant 500 mg arm compared with the fulvestrant 250 mg arm (6.5 vs. 5.5 months; HR 0.80; 95% CI 0.68 to 0.94; $p = 0.006$). Similar findings were reported for the post-anti-oestrogen population (8.6 vs. 5.8 months; HR 0.76; 95% CI 0.62 to 0.94; $p = 0.013$) and the post-aromatase

inhibitor population (5.4 vs. 4.1 months; HR 0.85; 95% CI 0.67 to 1.08; $p = 0.195$), although these findings were only significant for the post-anti-oestrogen population.

Secondary outcomes reported in the CONFIRM study include objective response rate (ORR), clinical benefit rate (CBR) and OS. The results suggested no statistically significant differences between fulvestrant 500 mg and 250 mg for these outcomes, although OS was numerically greater in the fulvestrant 500 mg group (25.1 vs. 22.8 months). Log rank analysis suggested a trend for improved OS in the fulvestrant 500 mg group (HR 0.84; 95% CI 0.69 to 1.03; $p = 0.091$). OS data from the CONFIRM trial were not mature, with 51% of mortality events occurring at the time of primary data cut-off for TTP. The manufacturer stated that it plans to re-analyse the OS data when 75% of all patients have died.

A total of 2443 AEs were reported by 483 (66%) of the 735 patients in the safety analysis set in the CONFIRM trial. Fifty-four patients (7%) reported a serious adverse event (SAE) including 11 patients (1%) who died due to an AE. Seventeen patients (2%) discontinued study treatment due to an AE. There were no notable differences in the incidence of AEs between treatment groups. The most common adverse events were injection-site pain (11.6%), nausea (9.7%) and bone pain (9.4%).

The manufacturer also provided health-related quality of life data taken from the CONFIRM study in which a total of 145 women completed the FACT-B questionnaire at baseline. No significant differences were detected between the fulvestrant 500 mg and 250 mg study arms.

Finally, the manufacturer noted the limitations of the CONFIRM study in the UK context because a high proportion (60%) of the patient population had visceral metastases. The manufacturer stated that patients with visceral metastasis have a poorer prognosis than those with other types of metastasis (for example, bone metastasis) and are commonly treated with chemotherapy in the UK.

2.1.2 FINDER-1 and FINDER-2 trials

The FINDER-1 study was a multi-centre, 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 ratio to receive either fulvestrant 500 mg, fulvestrant 250 mg or fulvestrant 250 mg with a loading dose.

The FINDER-2 study was a multi-centre, 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 ratio to receive either 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 ORR with secondary outcomes including CBR and TTP. The findings from these trials were broadly in favour of fulvestrant 500 mg compared with 250 mg.

2.1.3 Network meta-analysis

The manufacturer conducted a network meta-analysis in order to compare OS and TTP of fulvestrant 500 mg with the comparators listed in the final scope (see pages 74–118 of the manufacturer's submission for further details). Five RCTs including three of the other comparators (anastrozole, letrozole and exemestane) listed in the final 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; the manufacturer asserted that the inclusion of the post-aromatase inhibitor group 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 due to a lack of any relevant trials where 70% or more patients had hormone receptor positive advanced breast cancer in a post-anti-oestrogen population. Therefore, a secondary scenario analysis, as part of the cost-effectiveness analysis comparing fulvestrant 500 mg with exemestane, was undertaken by the manufacturer.

For the base-case network analysis, data on two outcomes were collected: OS 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 extrapolate OS. As hazard ratios in the CONFIRM trial were constant over time, the relative treatment effects of the alternative treatments were applied to the baseline treatment (fulvestrant 250 mg) using a pooled hazard ratio for OS estimated from the network meta-analysis. In the case of TTP, the log-normal distribution was identified by the manufacturer as the best-fitting distribution. As the assumption of constant hazard over time is not theoretically possible with the log-normal distribution, the relative treatment effects of alternative treatments were applied to the baseline treatment (fulvestrant 250 mg) using the relative pooled shape and scale parameters of the log-normal distribution.

A summary of the results of the network meta-analysis that were used in the economic model are presented in Table 1. The results presented by the manufacturer suggest that fulvestrant 500 mg improves OS when compared with fulvestrant 250 mg, anastrozole or letrozole, although the results are not statistically significant. However, statistically significant improvements in TTP were reported for fulvestrant 500 mg compared with fulvestrant 250 mg and anastrozole.

2.2 Evidence Review Group comments

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 appear to have been identified.

The ERG commented that the CONFIRM study was well-designed and that the clinical outcomes reported in this RCT and supporting phase II trials (FINDER-1 and FINDER-2) address all the relevant outcomes outlined in the final scope. However, it was also noted by the ERG that fulvestrant is currently most commonly used in clinical practice in England and Wales as a third or fourth endocrine therapy for advanced breast cancer, and then often

after an aromatase inhibitor. In the trials used as the basis for direct clinical evidence, fulvestrant was most commonly used as a first-line therapy for locally advanced or metastatic breast cancer in the post-anti-oestrogen group. Therefore, the ERG comments that the generalisability of the patient population to clinical practice may be questionable. The ERG also noted that, although the CONFIRM trial was carried out across 17 countries, no patients were recruited in the UK, which may also limit the generalisability of the clinical results. However, one clinical expert commented that 'the settings in which faslodex [fulvestrant] has been tested reflect the conditions in UK current practice'.

The ERG commented that it was satisfied with the statistical methodology utilised in the analyses of the primary and secondary endpoints of the CONFIRM trial. Several pre-defined subgroup analyses were undertaken by the manufacturer to investigate the consistency of any treatment effect across potential prognostic factors for TTP, including last therapy (post-anti-oestrogen vs post-aromatase inhibitor) prior to fulvestrant. The ERG highlighted that the EU licence for fulvestrant 500 mg is based on the patient having received previous anti-oestrogen therapy, although the ERG noted that it is not clear from the wording of the licence that eligibility for treatment is dependent on the last therapy received. Therefore, the ERG requested from the manufacturer that the TTP data from CONFIRM was split by: patients who had previously received an anti-oestrogen only; patients who had received an aromatase inhibitor only; and patients who had received both an anti-oestrogen and aromatase inhibitor (see appendix 2 of the ERG report for further details). The ERG noted that the results of the manufacturer's subgroup analysis for these prior therapy groups

[REDACTED]

[REDACTED]

[REDACTED] (in-confidence data presented in appendix 2 of the ERG report). The ERG noted that two thirds of the patients who received an anti-oestrogen appeared to be receiving fulvestrant as a first-line treatment for locally

advanced or metastatic breast cancer, which may be a factor in the improved results for this subgroup (compared with the post-aromatase inhibitor group).

In its critique of the network meta-analysis, the ERG noted that, with the exception of the CONFIRM, FINDER-1 and FINDER-2 trials, in the remaining trials, none of the patients had received a prior aromatase inhibitor. In addition, differences in the median age and prior endocrine therapies were noted. Therefore, the ERG considered that the population in the CONFIRM trial was heterogeneous and that it was not meaningful to treat the post-anti-oestrogen and post-aromatase inhibitor patients as though they were similar. The ERG suggested that the network meta-analyses should only include the post-anti-oestrogen patients from the CONFIRM, FINDER-1 and FINDER -2 trials. However, it was also acknowledged by the ERG that, by using a subgroup of the CONFIRM trial, the statistical power of the study is diminished. Overall, the ERG suggested that the advantages of including only post-anti-oestrogen patients (decreased heterogeneity) would outweigh the disadvantages (reduced statistical power of the CONFIRM trial).

In regards to the network meta-analysis of OS, the ERG noted that no adjustment had been made for the inclusion of the three-arm trials. The ERG re-ran the analyses after making this adjustment and found that it made little difference to the results presented. The ERG also commented that the baseline comparator used in the network meta-analyses should have been fulvestrant 500 mg rather than fulvestrant 250 mg. Therefore, the ERG requested that the manufacturer re-analysed the data, fitting fulvestrant 500 mg as the baseline comparator. The statistically significant difference found was when fulvestrant 500 mg was compared with megestrol acetate (which was not a comparator listed in the scope).

ERG exploratory analyses

As previously discussed, the ERG had concerns that the population of the CONFIRM trial differs to that of other trials included in the base-case network meta-analysis because it includes patients previously treated with either an anti-oestrogen or aromatase inhibitor. Therefore, the ERG re-ran the analysis

using data only from patients whose previous endocrine therapy was an anti-oestrogen (n = 423). The results were comparable to those obtained when the whole population of the CONFIRM trial was included in the analysis. All hazard ratios still favoured fulvestrant 500 mg over other treatments considered in the scope, although these were not statistically significant (see section 4.3 of the ERG report for further details).

In response to a request from the ERG, the manufacturer provided detailed Kaplan-Meier analysis results for post-progression survival, separately for patients who had previously received any aromatase inhibitor treatment and those who had not (anti-oestrogen patients) within both trial arms (fulvestrant 500 mg or 250 mg). A direct comparison of the post-progression survival experience showed no statistically significant differences between subgroups within both trial arms. The main consequence of this finding was that all differential benefit from the use of fulvestrant 500 mg is limited to the pre-progression phase. Therefore, the ERG concluded that examination of TTP data from CONFIRM was sufficient to establish a reliable estimate of overall survival gain from fulvestrant 500 mg.

For the TTP network meta-analysis, the ERG questions the assumption that the trials follow a log-normal distribution, due to the higher number of progression events occurring around 90 days followed by a 90-day period with relatively few new events. From 180 days onwards, there was a clear indication of a linear relationship between time and the cumulative TTP/PFS hazard. Therefore, the ERG split the estimation of TTP into two phases. For the first 180 days from randomisation, the CONFIRM Kaplan-Meier results would be used directly using the log-hazard ratios at 180 days. For the remaining period (180+ days), TTP was modelled using an exponential model calibrated using a landmark analysis.

The results of this analysis showed that there are no statistically significant differences in TTP between fulvestrant 500 mg and other treatments considered in the decision problem 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 the long-term patient experience) fulvestrant 500 mg results in statistically significant improvements in TTP compared with anastrozole and letrozole (see section 4.3 of the ERG report for further details).

As no post-progression survival advantage associated with fulvestrant 500 mg was identified by the ERG, it was necessary to transfer these TTP estimates accurately to OS gains. A compatible set of survival estimates (PFS, post-progression survival and OS) were prepared for fulvestrant 250mg patients, by calibrating a hazard ratio applied to the OS estimated for fulvestrant 500 mg patients which generated an OS gain equal to the corresponding estimated TTP/PFS gain. The same approach was used for anastrozole and letrozole since key clinical trials comparing anastrozole with fulvestrant 250 mg (which were powered for non-inferiority) demonstrated no statistically significant differences in TTP and OS. However, no trial data were available to verify any significant differences in TTP and OS between letrozole and fulvestrant (250 or 500 mg).

3 Cost effectiveness

3.1 *Cost effectiveness in the manufacturer's submission*

The manufacturer developed an excel-based cost–utility model, based on a time-in-state model structure. The model structure is similar to a Markov cohort model with three possible health states: pre-progression, post-progression and dead. 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 OS. All patients are assumed to be in the pre-progression health state at model entry (baseline). The duration of second-line hormonal treatment was 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. The final absorbing health state in the model is death, which patients can move to from either the pre-progression or the post-progression health state, capturing death from any cause. The model uses monthly cycles with a lifetime (13-year) horizon.

3.1.1 Clinical evidence

Results of the base case network meta-analysis for TTP and OS clinical effectiveness data were used to populate the economic model. For the base case analysis, comparator treatments included fulvestrant 250 mg, anastrozole and letrozole as per the network meta-analysis. The manufacturer used the overall CONFIRM trial (i.e. mixed) population in the analysis.

For adverse events, the manufacturer reports that it was not feasible to analyse the proportion of patients with Grade 3 or Grade 4 AEs because AEs were not consistently reported across trials included in the network meta-analysis. However, the manufacturer included SAEs within the model because there were sufficient data available on the number of SAEs to conduct a network meta-analysis. The SAE data used in the model included both treatment-related and treatment-independent events, because these were available for all the relevant RCTs used to derive the TTP and OS estimates in the base case analysis.

Table 1 summarises the clinical parameters used to populate the economic model.

Table 1 Clinical parameters used in the economic model

Network meta-analysis: overall survival hazard ratios vs fulvestrant 250 mg		
Treatment	Hazard ratio (95% CrI)	
Fulvestrant (500 mg)	0.84 (0.69 to 1.03)	
Anastrozole (1 mg)	1.02 (0.88 to 1.19)	
Letrozole (2.5 mg)	1.20 (0.83 to 1.74)	
Network meta-analysis: time to progression results		
Treatment	Scale Scale (95% CrI)	Log shape Median of posterior distribution (95% CrI)
Fulvestrant (250 mg) (base-line comparator)	1.676 (1.6 to 1.75)	-0.185 (-0.344 to -0.062)
	Difference in scale (95% CrI)*	Difference in log shape (95% CrI)*
Fulvestrant (500 mg)	0.229 (0.167 to 0.293)	-0.102 (-0.185 to -0.020)
Anastrozole (1 mg)	-0.094 (-0.189 to -0.004)	0.029 (-0.109 to 0.173)
Letrozole (2.5 mg)	0.045 (-0.140 to 0.231)	0.108 (-0.139 to 0.348)
Network meta-analysis serious adverse events results		
Treatment	Proportion of serious adverse events (95% CrI)	
Fulvestrant (250 mg)	9.1% (6.4% to 12.1%)	
Fulvestrant (500 mg)	10.2% (6.5% to 15.0%)	
Anastrozole (1 mg)	6.4% (4.1% to 9.7%)	
Letrozole (2.5 mg)	8.8% (3.6% to 20.2%)	
*If the log shape is equal for all treatments, the sign of the difference in scale shown indicates whether the treatment improves TTP/PFS more than the comparator i.e. if the difference in scale is positive then the treatment is better, if the difference in scale is negative the comparator performs better. If the 2.5th and 97.5th percentiles are of the same sign then the difference is statistically significant (assuming a constant shape)		
CrI, Credible Interval		

3.1.2 Utilities

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 in 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

elicited from a relatively small sample of the general public in the UK using the standard gamble technique (see pages 174–175 of the manufacturer's submission for further details). The study provided a utility value of 0.72 for pre-progression and 0.44 for the post-progression health states used in the economic model. Death was assigned a utility value of zero. Any disutilities associated with treatment-related AEs were not included in the model.

3.1.3 Costs

The following resource use and costs were included in the economic model:

- treatment costs for each hormonal treatment during the pre-progression phase
- hormonal treatment costs during the post-progression phase including supportive palliative care and chemotherapy
- costs associated with SAEs

Treatment costs – pre-progression

Total treatment costs, including drug and administration costs for each hormonal treatment relevant to the decision problem, are summarised in Table 2. No treatment-related monitoring costs associated with fulvestrant 500 mg or its comparators were included in the economic model (for further details see pages 183–192 of the manufacturer's submission).

Table 2 Summary of treatment costs included in the model (per monthly cycle)

Drug costs	Dose description, vial/pack	Price per vial/pack	Price per month (per 30.4 days)
Fulvestrant (250 mg)	1 x 5-ml intramuscular injection monthly, 50 mg/ml, net price 5 ml (250 mg)	£348.27	£348.27
Fulvestrant (500 mg)	2 x 5-ml intramuscular injection monthly plus additional dose 2 weeks later, 2 x 50-mg/ml, net price 5 ml (250 mg)	£522.41	£522.41
Anastrozole (1 mg)	1 mg daily, 28-tablet pack	£68.56	£74.48
Letrozole (2.5 mg)	2.5 mg daily, 28-tablet pack	£84.86	£92.18
Administration costs	Total cost for first month (per 30.4 days)	Total cost for subsequent months (per 30.4 days)	
Fulvestrant (250 mg)	£298	£79	
Fulvestrant (500 mg)	£377	£79	
Anastrozole (1 mg)	£193	£22	
Letrozole (2.5 mg)	£193	£22	

Treatment costs – post progression

The post-progression health state includes costs associated with subsequent treatments that a patient may receive after disease progression while on second-line hormonal therapy. In order to reflect clinical practice in England, treatment-skipping rules were applied to subsequent lines of treatments. The manufacturer included four potential subsequent treatment pathways in the economic model, including the following options:

- A) Third line hormonal therapy + supportive palliative care
- B) Chemotherapy + supportive palliative care
- C) Third line hormonal therapy + chemotherapy + supportive palliative care
- D) Supportive palliative care

The overall average cost per monthly cycle post progression was calculated as £1084, which was applied to each treatment arm for the proportion of patients in the post-progression health state (for further details see pages 192–196 of the manufacturer's submission).

Adverse-event costs

The model assumed that each SAE is associated with an average hospital stay of 5 days at a cost of £312.02, which was then weighted by the proportion of SAEs estimated in the network meta-analysis for each hormonal treatment considered in the scope.

3.1.4 Results

Table 3 summarises the results of the manufacturer's base case incremental analysis. The manufacturer used letrozole as the reference case because it was associated with the lowest total costs. Fulvestrant 500 mg was associated with the highest total quality-adjusted life years (QALYs) (1.487) followed by fulvestrant 250 mg (1.256), anastrozole (1.214) and letrozole (1.105). Based on an incremental analysis ranking of treatments, the base case results demonstrated that anastrozole and fulvestrant 250 mg were extendedly dominated by a linear combination of fulvestrant 500 mg and letrozole. The comparison of fulvestrant 500 mg and letrozole, resulted in an incremental cost-effectiveness ratio (ICER) of £31,982 per QALY gained.

The manufacturer conducted deterministic sensitivity analyses by varying key model input parameters from their low and high values (see pages 219–221 of the manufacturer's submission for further details). The key drivers of the cost-effectiveness results are the 95% credibility intervals for the scale and log shape for TTP and OS curves and 95% confidence intervals for the utility values assigned to the pre- and post-progression health states.

Table 3 Manufacturer's base case ICERs

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Letrozole	£18,836	1.105	–	–	–	–
Anastrozole	£22,467	1.214	£3631	0.109	£33,286	ED
Fulvestrant 250 mg	£25,603	1.256	£3136	0.042	£44,763	ED
Fulvestrant 500 mg	£31,075	1.487	£5472	0.232	£31,982	£31,982
ED, extended dominance; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.						

The manufacturer also conducted six scenario analyses to assess the impact of key assumptions made in the base-case analysis (see pages 223–229 of the manufacturer's submission). These scenarios included:

- expanding the patient population to post-anti-oestrogen/aromatase inhibitor to enable the inclusion of exemestane into the network meta-analysis
- cost of administration of fulvestrant 500 mg and 250 mg using alternative proportions of administration in the primary care setting
- cost of post-progression using alternative mix of chemotherapies
- cost of post-progression eliminating treatment skipping
- discounting costs and benefits at 0% and 6%
- altering the time horizon.

In summary, exemestane (first scenario only), anastrozole and fulvestrant were all extendedly dominated by a linear combination of fulvestrant 500 mg and letrozole in all scenarios. The comparison of fulvestrant 500 mg and letrozole resulted in a range of ICERs from £30,656 to £43,025 per QALY gained.

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

per QALY gained, letrozole had a 41% probability of being cost effective, anastrozole had a probability of 34% and fulvestrant 250 mg had a probability of 5%.

3.2 Evidence Review Group comments

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 relates to the use of data from the network meta-analysis, which includes patients from the CONFIRM trial who had previously been treated with an aromatase inhibitor. The ERG considered it more appropriate to base the model on those patients who had previously received anti-oestrogen therapy.

The ERG noted several criticisms in relation to the design of the manufacturer's model, which is based on separate parametric models of the time from randomisation to TTP and OS. The ERG commented that when different statistical functions 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, it is possible for projected estimates of TTP to exceed the corresponding estimates of OS. Without a forced alteration in the model, the estimated post-progression survival for both fulvestrant arms would take negative values from year 10 onwards, with no inbuilt error-checking mechanisms within the model to detect such anomalies. Overall, the ERG concludes that the design of the manufacturer's economic model is unlikely to provide a robust basis for projecting survival beyond the observed data.

The ERG again commented that the log-normal parametric model applied to TTP data fails to adequately represent the CONFIRM trial data on which it was calibrated after directly comparing the log-normal estimate of TTP for fulvestrant 500 mg used in the economic model with Kaplan-Meier results obtained from the CONFIRM trial (see pages 78–79 of the ERG report for further details). Therefore, it is suggested that the manufacturer's estimate of

TTP does not provide a robust basis for projecting the available trial data for the remainder of patients' lifetimes.

The ERG reported a few minor errors in relation to the cost data used in the manufacturer's model. Firstly, the manufacturer's model does not account for wastage of part-used dispensed packs at the time of progression. The ERG also questioned the use of expert opinion for pre- 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, 2009). The ERG also commented that the manufacturer's model limits drug-related AEs to SAEs only. The manufacturer's approach of applying a single average cost of UK hospital admissions is simplistic and inappropriate for costing AEs associated with treatment complications in advanced breast cancer. The ERG calculated an alternative estimate of £3147 per episode, compared with the estimate in the manufacturer's model of £1605 per episode. Overall, the ERG stated that making all of these modifications to the model increases the ICER in all cases but, because each change represents only a small element of the total cost, the increases are small.

Finally, the ERG noted an error in the utility values assigned to the pre- and post-progression health states in the manufacturer's economic model. The age parameter used in the analysis used to generate utility values in Lloyd et al. (2006) referred to the age of 100 participants in the valuation exercise and not to the age of 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 sample used). Using ERG estimated values of 0.7733 for time in TTP and 0.4964 for time in post-progression reduces the ICER for fulvestrant by £2700 per QALY gained compared with the other comparators.

ERG exploratory analyses

The ERG made eight separate modifications in order 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 substituting effectiveness data from the anti-oestrogen sub-population in the CONFIRM trial in place of the whole trial sample. The ERG presented detailed deterministic results separately for the manufacturer's base case scenario using the whole CONFIRM population and for the anti-oestrogen sub-population (see pages 89–93 of the ERG report for further details).

In summary, based on the full CONFIRM trial population, the calculated deterministic cost-effectiveness results showed that fulvestrant 250 mg was extendedly dominated by the other comparators while the ICERs for anastrozole vs letrozole and fulvestrant 500 mg vs anastrozole are both close to £30,000 per QALY gained. The deterministic cost-effectiveness analysis based on the anti-oestrogen subgroup from CONFIRM and 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.

3.3 *Further considerations following pre-meeting briefing teleconference*

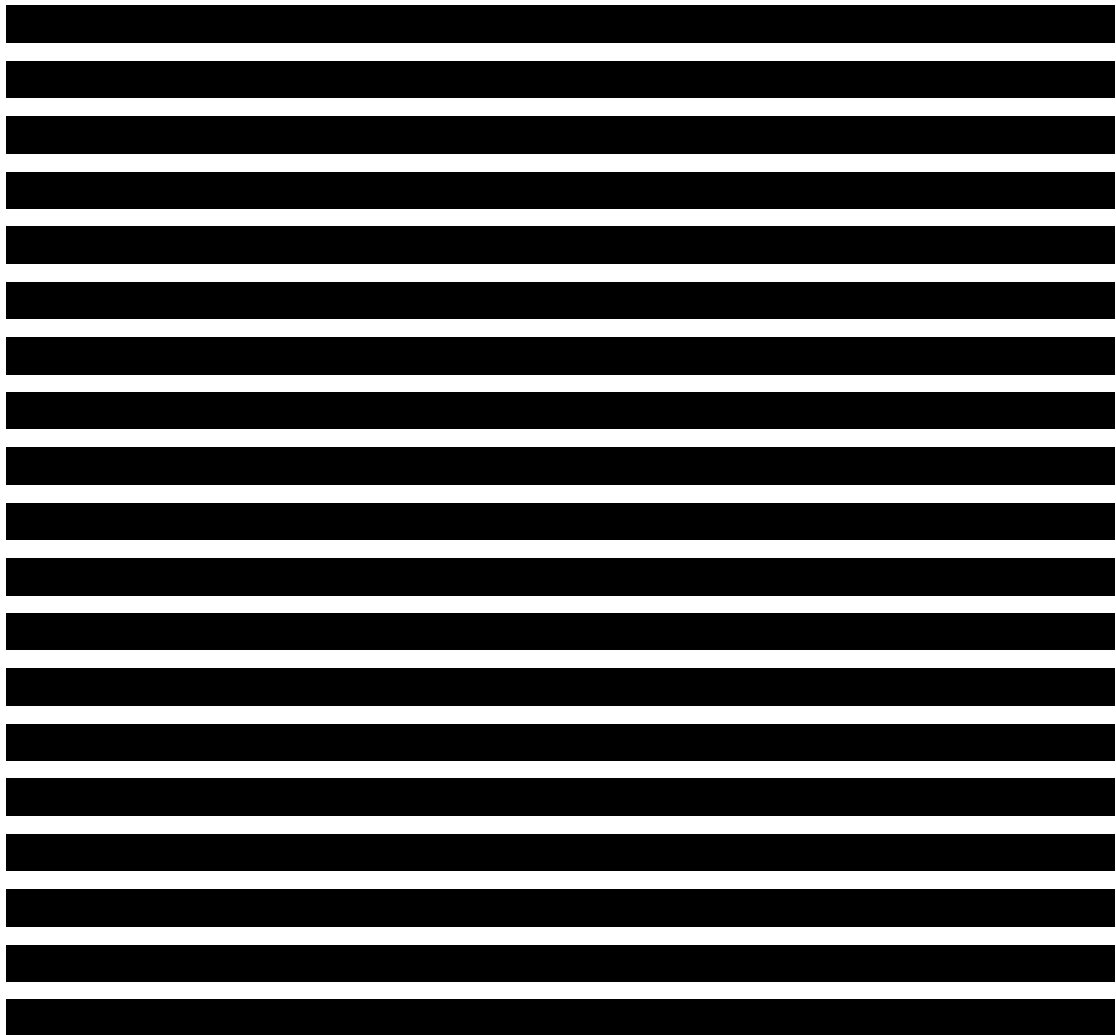
Baseline characteristics of trials included in network meta-analyses

Following the pre-meeting briefing teleconference, the lead team requested that the ERG provide additional commentary on the baseline characteristics of the trials included in the network meta-analyses used to estimate TTP and OS. Specifically, the ERG provided further details of the following baseline variables:

- WHO performance status
- Visceral involvement/metastases
- Proportion of patients known to be oestrogen-receptor positive (ER+)
- Proportion of patients previously treated with chemotherapy

- Proportion of patients with early/advanced breast cancer previously treated with an anti-oestrogen

In summary, across the eight trials included in the network meta-analyses, all included trials that reported it had a baseline WHO performance score of ≤ 2 ; baseline visceral involvement ranged from 18.9% (Osborne 2002) to 80.4% (FINDER-2); patients with known ER+ status ranged from 66.9% (Buzdar 1996/98) to 100% (CONFIRM, FINDER-1 and -2); the proportion of patients previously treated with chemotherapy ranged from 35.6% (Buzdar 2001) to 72.5% (FINDER-1) and; the proportion of patients with early breast cancer previously treated with an anti-oestrogen ranged from 35.1% (Buzdar 2001) to 59.8% (Osborne 2002); the proportion of patients with advanced breast cancer previously treated with an anti-oestrogen ranged from 19.9% (CONFIRM) to 56.3% (Howell 2002).



Appendix A: Sources of evidence considered in the preparation of the pre-meeting briefing

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

- Fleeman N, Bagust A, Boland A et al. (2011) Fulvestrant for the treatment of locally advanced or metastatic breast cancer: a single technology appraisal. Liverpool Reviews and Implementation Group, The University of Liverpool.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- AstraZeneca

II Professional/specialist, patient/carer and other groups:

- British Cancer Care
- Royal College of Pathologists
- NCRI/RCP/RCR/ACP/JCCO

C Additional references used:

National Institute for Health and Clinical Excellence (2009). Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidance/CG81