NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Fulvestrant for the treatment of locally advanced or metastatic breast cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
AstraZeneca	**Generalisability of Pivotal RCT** ***'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' (Section 3.21)*** Although the CONFIRM trial did not include UK patients, of the 17 countries involved, 10 were European. Furthermore, it is worth highlighting that 95% of the CONFIRM trial population were Caucasian. This makes the CONFIRM trial's clinical results generalisable to a UK population and was the basis of the licence approval across the UK and Europe.	Comment noted. This sentence has been amended to say that: 'The ERG also noted that no patients were recruited to CONFIRM from the UK.'
AstraZeneca	**AI therapy for EBC/ABC** ***'.....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' (Section 4.4)*** AstraZeneca acknowledges there is a body of clinicians for whom AIs are the adjuvant treatment of choice for a large proportion of patients. Nonetheless, significant regional variations exist in protocols and prescribing practices on the uptake of adjuvant AIs; leading to a significant (21.5%) proportion of patients still being initiated on tamoxifen. See charts below [**Reference**: HMSL data (Cegedim Strategic Data UK)]	Comment noted. Section 4.4 notes that: '…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…'

Consultee	Comment	Response
AstraZeneca	**Role of Tamoxifen (AO) in treatment pathway** ***'The use of tamoxifen in clinical practice as sole adjuvant treatment or as a first-line treatment for new locally advanced or metastatic breast cancer is diminishing, apart from for the small proportion of women who are unable to tolerate an aromatase inhibitor……..' (Section 4.4)*** There continues to be high level of patients recurring on tamoxifen. This is due to: 1. The time lag between initiation and recurrence of patients on tamoxifen 2. The continuing role for tamoxifen as adjuvant therapy in selected patient populations **1. <u>Initiations vs. recurrence</u>** While AstraZeneca is in agreement that the **<u>initiation</u>** of anti-oestrogen (tamoxifen) therapy as sole adjuvant treatment (currently 21.5% of adjuvant initiations) [1] is diminishing, the current proportion of patients (as of Q4 2010) **<u>recurring</u>** on tamoxifen is approximately 60% (based on information from 80 oncologists and 1900 breast cancer patients).[2] This level of recurrence is likely to remain stable for a number of years, as it represents only a decrease of 9% since Q1 2006.[2] There is a time lag between the initiation of patients on tamoxifen and the time of recurrence breast cancer. According to the recently published 15 year update of the EBCTCG meta-analysis,[3] the time to recurrence on tamoxifen has yet to reach a median point. On this basis, it is likely to take at least a decade until the recurrence ratio begins to reflect the current new initiations ratio. Please see charts below. Charts not reproduced here. **2. <u>Tamoxifen Patient Population</u>** NICE CG80[4] and a recent advisory board of clinical experts acknowledge and endorse that there will always be a role for adjuvant tamoxifen in a number of patient groups. (i) Low risk adjuvant patients who initiate, and continue, on tamoxifen (ii) Patients with contraindications to AIs (iii) Patients unable to tolerate AIs **<u>References</u>** 1. HMSL data (Cegedim Strategic Data UK) 2. Synovate European Oncology Monitor (Synovate Healthcare) 3. Early Breast Cancer Trialists Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687-1717 NICE CG80: Early and locally advanced breast cancer: diagnosis and treatment (2009)	The Committee also considered the the small subgroup of women who are unable to tolerate treatment with any aromatase inhibitor. Please see FAD section 4.16.

Consultee	Comment	Response
AstraZeneca	**Results of Pivotal RCT** ***"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." (Section 4.6)*** For both these sub-groups (post AO and post AI) in CONFIRM, the TTP/PFS was in favour of fulvestrant 500mg. It is also important to highlight that the CONFIRM trial was powered to detect a statistically significant difference between fulvestrant 500mg and 250mg for the full trial population and not for the subgroups.	Comment noted. Section 4.6 has been amended to include: '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.'
AstraZeneca	**Fit of Parametric Survival Models** "***However, the Committee concluded that, because of the issues identified by the ERG around the fit of the parametric survival models used by the manufacturer, there was high uncertainty around the validity of these results***." ***(Section 4.7)*** This statement is factually incorrect, as it implies that the ERG raised issues with both the fit of the parametric model for TTP and OS **to the data**. The issue that the ERG identified regarding the standard parametric modeling approach used by the manufacturer for overall survival was regarding the uncertainty with respect to the projection rather than the fit to the data, as highlighted by the following comment made in the ERG report: "*Although a standard parametric model may be identified which appears to be a* ***reasonable match to the available data****, there must be serious uncertainty that projections of OS beyond the period of observation may be seriously over or under-estimated due to the complex risk changes that are likely to apply at later times*" (Section 5.5.1, Page 79) Please amend the last sentence in 4.7 to state that it relates to TTP and add a separate statement regarding the ERG's comments about the manufacturer's modeling approach used for overall survival.	Comment noted. Section 4.7 of the FAD has been amended accordingly.

Consultee	Comment	Response
AstraZeneca	**Results of Network meta-analyses** ***"The Committee also commented that the results of the network meta-analyses indicated better outcomes in terms of overall survival and TTP for letrozole 0.5 mg (which is unlicensed for this indication) compared with letrozole 2.5 mg (which is licensed) despite the results of two other trials (Dombernowsky et al. 1998; Gershanovich et al. 1998) that were excluded from the network meta-analyses, which showed superiority of letrozole 2.5 mg over the 0.5 mg dose" (Section 4.9)*** AstraZeneca would like to emphasise that trial results are not taken into account during the critical appraisal and selection process. Trials included in the network meta-analysis are chosen solely based on their study design and quality. 1. In the base case analysis only one trial involving letrozole (Buzdar 2001) met the inclusion criteria. The trials by Dombernowsky et al. 1998 and Gershanovich et al. 1998 did not meet the ER+ status criterion and were therefore excluded. However, relaxing the inclusion criterion to 'at least 50% HR+ known status' enabled a scenario analysis; which included a wider range of studies (including Dombernowsky et al. 1998 and Gershanovich et al. 1998) but had limited impact on the letrozole 2.5mg OS Hazard Ratios vs. fulvestrant 250mg (HR 1.20 base case vs. 1.14 scenario analysis) Please refer to Tables B34 and B96 in the MS. Although the results from Buzdar et al. 2001 suggest that letrozole 0.5mg performs better than letrozole 2.5 mg (*median TTP was reported as 6months for letrozole 0.5mg, compared to 3months for letrozole 2.5mg),* it is worth noting the authors comment that there was no significant difference in results between the two letrozole doses. There seems to be no clear reason, beyond random play of chance, why the study showed a greater benefit for the lower dose of letrozole.	Comment noted. Section 4.9 has beenamended as follows: '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.'

Consultee	Comment	Response
AstraZeneca	**Position of Fulvestrant in UK clinical practice** ***'The Committee concluded that the most likely position of fulvestrant in UK clinical practice would be as third-line or fourth-line treatment after therapy with aromatase inhibitors and/or an anti-oestrogen therapy. However, on the basis of the manufacturer's confirmation of the licensed position for fulvestrant (section 4.3) it considered that third-line or fourth-line use was not within the remit of this appraisal.' (Summary of key conclusions - Section 4.4)*** **1. Line of therapy** Much of the current use of fulvestrant, in 3rd and 4th line, is outside of the licensed position in the UK. This usage is driven by the heritage of the drug, whereby supporting trial data for the 250mg dose (studies 0020 and 0021) demonstrated equivalence (non-inferiority) of fulvestrant 250mg over anastrozole and as a result clinicians reserved use to later lines of therapy. However, the CONFIRM study demonstrated the significantly superior efficacy of fulvestrant 500mg over the previous 250mg dosage in the second line setting post tamoxifen (see note 2 below). This Technology Appraisal is to review and establish the clinical efficacy and role of the 500mg dosage of fulvestrant in this setting. It is inappropriate for the historical clinical experience of fulvestrant 250mg in later lines of therapy to influence the evaluation of fulvestrant 500mg in the second line setting and as such, it should not influence this review or decision of the appraisal committee. Fulvestrant **500mg** should be considered on its own merits: based on clinical evidence supported by the network meta-analysis and the manufacturer's base case economic model, alongside the review carried out by Liverpool ERG. **1. Use post anti-oestrogen vs. aromatase inhibitors** AstraZeneca would like to clarify that fulvestrant is only licensed for use following relapse or progression on or after anti-oestrogen therapy (that is, tamoxifen) and this does not include use after aromatase inhibitors. There are no ongoing trials which will result in a license in a post-AI patient population. It should also be noted that the SOFEA study is neither an AstraZeneca study nor a regulatory study and will therefore not lead to any changes to the licence for fulvestrant.	Comment noted. Fulvestrant has been appraised within its licensed indication; confirmed by the manufacturer to be 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. This summary table has been amended to include the marketing authorisation of fulvestrant.

Consultee	Comment	Response
AstraZeneca	**Eligibility criteria for trials included in network meta-analyses** ***"…The Committee was also aware that no firm eligibility criteria for trials included in the network meta-analyses could be produced by the manufacturer" (Summary of key conclusions - Section 4.9)*** This statement is incorrect, as it implies AstraZeneca did not follow rigorous methods in carrying out the systematic review and network meta-analyses. There were firm inclusion/exclusion criteria set for the search strategy for the base case analysis. These can be found in Table B22 of the manufacturer's submission [MS] (Please see page76, section 5.7.2 of the MS). Please also refer to the ERG report which states: *"The MS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies"* (section 4.1.2 (p 27)). The ERG concluded that they were *"satisfied with the clinical-effectiveness literature review process as described in the MS"* (page 27 of the ERG report) In setting the inclusion/exclusion criteria, a number of considerations were taken into account: **1. Oestrogen receptor positive status (ER+ status)** As oestrogen receptor positive status (ER+ status) is the most important factor determining sensitivity of breast cancer to endocrine treatment in current clinical practice, it was decided that the level of known ER+ status in the trial population would be the fairest basis of comparison amongst the comparator molecules and should therefore be set as an important inclusion criterion (clarification provided below) **2. Other factors** Factors influencing heterogeneity other than ER+ status could not be mitigated against without excluding a significant number of trials. Setting other inclusion/exclusion criteria, for example, around age of trial or the amount of previous chemotherapy would result in insufficient trials for any meaningful comparisons to be drawn between comparators - anastrozole, exemestane, letrozole and fulvestrant 250mg (as defined in the final scope).	Comment noted. The summary table has been amended accordingly.

Consultee	Comment	Response
	Clarification on ER+ Status Criterion*	

Application of a strict criterion of 100% ER+ status would have resulted in the exclusion of all trials other than AstraZeneca trials CONFIRM, FINDER I and II, from the analysis.
Thus, it was necessary to determine a level at which the criterion could be set, which would permit the inclusion of comparators other than fulvestrant 250mg for the submission while at the same time restrict the introduction of too high a level of heterogeneity into the pool of trials. Following a broad consultation with clinical experts (which failed to produce a genuine consensus), a decision was made to set the level as 'at least 70% known ER+ status'.
*Section 5.7.2.1 (p77-78) of the MS provides the reasoning behind setting 'at least 70% ER+ status' as a criterion.

This was believed to sufficiently permit the inclusion of a wider range of studies whilst limiting the level of heterogeneity across the different trial populations.
Please see table below for the % ER+ status of all trials on the comparators.

% ER+ status of all trials on the comparators

				Base case analysis HTA		Scenario analysis	
Trials	Previous treatment %AO / %AI	Treatment	Treatment	% of known ER+	Eligible for base case	HR≥50%	Eligible
CONFIRM	57%AO / 43%AI	Faslodex 500mg	Faslodex 250mg	100%	Yes	Yes	Yes
FINDER I	45%AO / 76%AI	Faslodex 250mg	Faslodex 500mg	100%	Yes	Yes	Yes
FINDER II	59%AO / 66%AI	Faslodex 250mg	Faslodex 500mg	100%	Yes	Yes	Yes
Howell 2002 Study 20	100%AO	Faslodex 250mg	Anastrozole 1mg	76%	Yes	Yes	Yes
Osborne 2002 Study 21	100%AO	Faslodex 250mg	Anastrozole 1mg	87%	Yes	Yes	Yes
Buzdar 1996/1998	100%AO	Anastrozole 1mg/10mg	MA 160mg	70%	Yes	Yes	Yes
Lundgren 1989	100%AO	AG 500mg	MA 160mg	71%	Yes	Yes	Yes
Buzdar 2001	100%AO	Letrozole 0.5/2.5mg	MA 160mg	81%	Yes	Yes	Yes
EFECT (Chia 2008)	100%AI	Faslodex 250 mg	Exemestane 25mg	98%	No - post AI pop	Yes	Yes
Kaufmann 2000	100%AO	Exemestane	MA 160mg	68%	No - ER+ criteria	Yes	Yes
Dombernowsky 1998	100%AO	Letrozole 0.5/2.5mg	MA 160mg	57%	No - ER+ criteria	Yes	Yes
Gershanovich 1998	100%AO	Letrozole 0.5/2.5mg	AG 500mg	36%	No - ER+ criteria	Yes	Yes

Consultee	Comment	Response
AstraZeneca	***"The Committee noted that this inclusion criterion was relaxed to include trials with at least 70% of patients with oestrogen-receptor-positive cancer, which resulted in exemestane being excluded as a comparator" (Section 4.9)*** This statement is misleading as it gives the impression that AstraZeneca chose to relax the criterion in order to exclude exemestane. The rationale for relaxing the ER+ criterion was to enable the inclusion of studies with comparators other than fulvestrant 250mg. Relaxing the criterion further to **at least 50% hormonal receptor positive (HR+) status** (as in the scenario analysis) permits the inclusion of exemestane data but also increases the heterogeneity of the studies and results in further uncertainty. 'At least 70% known ER+ status' was therefore chosen in the base case analysis so as to limit the level of potential additional heterogeneity and uncertainty but as a result exemestane could not be included. Please see Scenario A, Section 6.7.9 of the MS.	Comment noted. Section 4.9 and the summary table have been amended accordingly.
South Staffordshire PCT	Firstly, I as a formal consultee I agree with the comments made by CSAS in relation to the evaluation of the evidence. My comments however were in relation to how this service might be commissioned and delivered and to raise the potential additional costs that might impact on cost effectiveness. Fulvestrant in its licensed indications will if approved by NICE potentially be used in patients under specialist cancer care. Fulvestrant is not cytotoxic chemotherapy and therefore isn't specifically excluded from PbR Tariff, however as the costs are greater than 1.5 times the tariff income, Acute Trust providers may seek to negotiate PCO's funding as if it were excluded. There is therefore potential for fragmentation and guidance on the funding arrangements would be welcome to ensure consistency.	Comment noted. 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.

Consultee	Comment	Response
	If the drug is approved and provided via an Acute Trust Cancer service , and agreed as a PbR exclusion, the drug cost will be subject to VAT, increasing the cost by 20% for the commissioner. This cost should in our opinion be included in the cost-effectiveness analysis as this is what we will be expected to pay. In addition consideration needs to be given as to where ongoing doses will be given. If patients are receiving other chemotherapy, it may be cost-effective for this to be given in the clinic as part of the same day-case or outpatient appointment. If dedicated outpatient appointments are needed for this the cost will be around £1500 for the first year and £1200 thereafter. This too needs to be factored in to the cost-effectiveness analysis. Patient experience also needs to be taken into account and it may be undesirable or impractical for some patients in rural settings to travel to hospital on a monthly basis. Some GPs may be prepared to prescribe and administer but others won't.If prescribed by a GP on an FP10, the VAT will be zero rated and represent 20% saving to the commissioner, but there may be a demand for the GP to be paid under a local enhanced service to administer it. Nonetheless this is likely to be less expensive than a hospital outpatient appointment. Services may be fragmented however as some GP;s will do this whilst others won't. (such is the nature of LES's) Whilst NICE do not routinely consider commissioning arrangements, consideration perhaps should be given to the "Homecare Sector", through a competitive tendering procurement exercise it may be possible for this to be provided to patients in their own homes, zero rated for VAT , and at a cost again lower than an out patient setting.	Comment noted. Section 5.5.9 of the NICE Methods Guide specifically explains that: 'Value added tax (VAT) should be excluded from all economic evaluations but included in budget impact calculations at the appropriate rate (currently 17.5%) when the resources in question are liable for this tax.'

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Breakthrough Breast Cancer	**Has all of the relevant evidence been taken into account?** Approximately two thirds of women with breast cancer are diagnosed with ER+ breast cancer and could potentially benefit from fulvestrant, an oestrogen receptor antagonist and selective oestrogen receptor down regulator. A significant proportion of breast cancer patients will develop advanced and metastatic disease and treatment options for these women are limited. This drug gives an additional treatment option for women living with advanced or metastatic disease. As metastatic breast cancer is not curable, it is essential that treatment options which could delay progression or improve survival are made available for this patient group. Patients typically have limited treatment options in the metastatic setting and therefore the need for safe and effective new medicines in this patient group is relatively urgent. As the committee states, fulvestrant was found to extend life by at least 3 additional months compared to the currently used aromatase inhibitors anastrazole and letrozole and increased time to progression compared to anastrazole. Delaying time to progression and knowing there are active hormonal treatment options available is very important to the women we speak with. Delayed time to disease progression can improve the quality of life of these women. With fulvestrant patients can expect symptom control, which brings with it improved quality of life, including social functioning (e.g. continuing to work, maintaining relationships and the ability to participate in activities such as going on holiday) and spending more quality time with family and friends. Fulvestrant at 500mg is well-tolerated[1]. The appraisal committee heard from a patient taking fulvestrant that the disadvantages of monthly injections and the side effects of fulvestrant were outweighed by the benefits of remaining fit and well. In addition, the monthly administration of the drug enables patients to have regular communication with their specialist team.	Comments noted. The Committee considered all the available evidence for the clinical and cost effectiveness of fulvestrant. 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 recognised the importance of additional treatment options for post-menopausal women with locally advanced or metastatic breast cancer. (See FAD section 4. 2) Due to limitations within the evidence base, the Committee concluded that there was uncertainty around the results from the manufacturer's network meta analysis in which fulvestrant was compared with aromatase inhibitors (section 4.9).

[1] Di Leo A, Jerusalem G, Petruzelka L *et al.*(2009) CONFIRM: Phase III, randomized, parallel-group trial comparing fulvestrant 250mg vs fulvestrant 500mg in postmenopausal women with oestrogen receptor-positive advanced breast cancer. *Cancer Res,* 69 (24 Suppl): Abstract nr 25.

Nominating organisation	Comment	Response
	The importance of delayed progression and improved survival for women with advanced and metastatic breast cancer must not be underestimated. Although we recognise that fulvestrant does not meet all of the criteria for special consideration as an end of life treatment, we believe that the benefits it would bring to patients should be fully considered. When women are no longer benefiting from active hormonal treatments often the only option left for them is chemotherapy. Many women are keen to delay chemotherapy in favour of other treatments for as long as possible, as the side effects and disruption to their lives associated with chemotherapy can have a significant impact on their quality of life. The committee concluded that patients value having another treatment option after aromatase inhibitors and anti-oestrogen therapies because of its value as a treatment and also because it can delay chemotherapy. NICE guidance recommends aromatase inhibitors as adjuvant treatment for most postmenopausal women with oestrogen receptor positive early breast cancer. If a woman who has received aromatase inhibitors goes on to develop advanced or metastatic disease she will not usually be offered aromatase inhibitors again, further reducing her already limited treatment options. Although this appraisal considers the use of fulvestrant following tamoxifen but not aromatase inhibitor treatment, it is important to note that fulvestrant is most commonly used after aromatase inhibitors. The appraisal 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, which was outside the remit of this appraisal. It is worth noting that the clinical specialist the committee consulted stated that there is little or no clinical evidence about the optimal treatment sequence for advanced breast cancer beyond first-line treatment. We would welcome appraisal of use in this setting as it could provide women with a much needed treatment option.	The Committee concluded that fulvestrant did not fulfil the end-of-life criteria because fulvestrant is indicated for patients with a life expectancy of more than 24 months. (Section 4.18) The manufacturer confirmed that fulvestrant is licensed 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. The Committee considered that the most likely position of fulvestrant in UK clinical practice would remain as a third or fourth line treatment after aromatase inhibitors and/or an anti-oestrogen therapy. However, on the basis of the manufacturer's confirmation of the licensed position for fulvestrant (section 4.3), the Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal.(Section 4.4) The Committee concluded that the most plausible ICER for fulvestrant compared with anastrozole was £35,000 per QALY gained but noted the considerable uncertainty around this estimate. It 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. (Section 4.19)

Nominating organisation	Comment	Response
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We are disappointed that the Appraisal Committee is unable to recommend fulvestrant for the treatment of locally advanced or metastatic breast cancer. We acknowledge that the cost per QALY gained is relatively high in this setting. However, we understand that the manufacturer is attempting to set up an access scheme which could potentially reduce the cost per QALY to a more acceptable level. Fulvestrant is more commonly used as a 3rd or 4th line treatment when aromatase inhibitors are no longer effective, than in the place of aromatase inhibitors as reviewed here. Use following aromatase inhibitor failure is often in place of chemotherapy. Although fulvestrant has a high cost per QALY compared to aromatase inhibitors it would be useful to compare the cost of fulvestrant to the cost of chemotherapy. As mentioned previously, there are currently very few options for women with advanced and metastatic breast cancer and fulvestrant could have a large positive impact on their quality of life. The importance of this should not be underestimated. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** It is disappointing that the committee is unable to recommend fulvestrant 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. There are very limited treatment options for these women and as a patient organisation, Breakthrough Breast Cancer would like to emphasise the importance of further treatments for this group.	Comments noted. On the basis of the manufacturer's confirmation of the licensed position for fulvestrant (section 4.3), the Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal (Section 4.4).

Nominating organisation	Comment	Response
	We accept that the cost per QALY gained is relatively high compared to aromatase inhibitors. We hope that an access scheme may bring this down making fulvestrant more cost effective. We would welcome appraisal of fulvestrant in the setting in which it is most often used – following disease progression on aromatase inhibitors. If this drug is not made available for use by the NHS the implication is that active treatment by hormone therapy will cease following completion of aromatase inhibitor therapy. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None of which we are aware.	Comment noted. No approved patient access scheme was submitted for the technology being appraised. NICE can only make recommendations according to the marketing authorisation of the technology. 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. Therefore, appraising fulvestrant following disease progression on aromatase inhibitors was not within the remit of this technology appraisal.
Royal College of Nursing	**Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with metastatic breast cancer. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comments noted.

Nominating organisation	Comment	Response
	Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add at this stage. The RCN would welcome guidance to the NHS on the use of this health technology. **Are there any equality related issues that need special consideration that are not covered in the ACD?** We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comments noted. Comments noted. 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. Please see FAD section 4.20.
The Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO)	**Has all of the relevant evidence been taken into account?** We believe that all the relevant evidence had been taken into account. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	Comments noted.

Nominating organisation	Comment	Response
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The provisional recommendations are sound and a suitable basis for guidance to the NHS. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** In the opinion of our experts there are no aspects of the recommendations that would be discriminatory.	Comments noted.

Comments received from commentators

Commentator	Comment	Response
Commissioning Support, Appraisals Service (CSAS)	We are in agreement with the recommendations in the ACD not to recommend fulvestrant for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice. • **This technology is not a cost effective use of NHS resources.** The committee concluded that the ICER for fulvestrant in its licensed dose was likely to be at least £35,000 per QALY gained compared with the aromatase inhibitor anastrozole. However, considerable uncertainty remained regarding this estimate. • **Unit costs of fulvestrant are significantly higher than current standard** treatment. The cost of fulvestrant is currently £1,044.82 for the first month, and £522.41 in subsequent months (excluding VAT). This is based on BNF 61 prices for a 250mg prefilled syringe. The manufacturer reports that this pack size will no longer be available after 2012 due to the licensed dose now being 500mg monthly. This may affect costs. This compares to a cost for anastrozole 1mg daily of £74.48 per month. • **The relative clinical effectiveness of fulvestrant compared to aromatase inhibitors is uncertain.** There are no RCTs directly comparing the licensed dose of fulvestrant (500mg) against aromatase inhibitors (AIs). A network meta-analysis conducted by the manufacturer to allow these comparisons to be made indirectly suggested no significant differences in overall survival between fulvestrant and the AIs anastrozole and letrozole. Fulvestrant 500mg may offer a longer time to progression (TTP) compared to anastrozole however, there was heterogeneity between the studies included and limitations to the statistical methods used which meant that there was a high degree of uncertainty about the reliability of these results.	Comments noted.

Commentator	Comment	Response
	• **Evidence submitted by the manufacturer does not reflect current UK clinical practice.** In the UK, fulvestrant is considered as a third or fourth line treatment after aromatase inhibitor treatment. This use is outside the current marketing authorisation and therefore outside the remit of this technology appraisal. It is therefore unclear where fulvestrant would fit in the care pathway • **The exact number of patients who would be eligible for fulvestrant in its licensed indication is uncertain, but is likely to be small.** The manufacturer estimates that 2,200 women would be eligible under the existing license. Clinical advice offered to NICE suggested that most postmenopausal women now receive an aromatase inhibitor as adjuvant hormone therapy for early breast cancer or as first-line treatment if presenting with advanced breast cancer. This limits the use of fulvestrant under its current license. • **There were limitations to the quality of the evidence:** There were no RCTs comparing the licensed dose of fulvestrant against aromatase inhibitors. A network meta-analysis was conducted by the manufacturer to allow these comparisons to be made indirectly, but there were limitations to the methods used, including possible bias from the selection of the trials, heterogeneity between the trials included, and problems with the statistical methods used. These limitations reduce the reliability of the results of these analyses. • **Fulvestrant does not offer any improvement in overall survival, nor does it meet the criteria for end of life considerations.** There is no evidence indicating an increase in survival.	Comments noted.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	We are in agreement with the present NICE recommendation and are in line with our present policy agreed at our Medicines and Technology Board. This decision was made on the grounds that this treatment was no more effective than the other treatment options recommended within NICE guidance for this indication. It must be noted that two local cancer networks have recommended its use (one at third treatment option in both post and pre-menopausal women and the second one in post menopausal and ER+ve, with advanced/ metastatic breast cancer patients and who have the following: - have relapsed on aromatase inhibitor therapy in advanced disease. - patients with severe joint pains exacerbated by aromatase inhibitor therapy. - patients with compliance issues (swallowing problems). - Patients in whom certainty of administration is an advantage. And there is agreement by local Breast MDY that initiation of Fulvestrant is the best treatment option available to the patient. Clearly there is a need to a single recommendation that we can commission for all out patient population.	Comments noted.
	3	It is clear that this appraisal will not reflect current clinical practice as already confirmed within this document that it is generally used 3rd or 4th line. This is confirmed in this our area where a cancer network is recommending it 3rd line. It was noted that the Finder trial only included Japanese patients and questioned whether these results would be representative to patients within the UK. It is noted that there are no published RCTs that have compared high dose fulvestrant against aromatase inhibitors for postmenopausal women with oestrogen receptor positive advanced breast cancer (locally advanced or metastatic) which has progressed or relapsed during or after other anti-oestrogen treatment.	Comments noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		So only indirect comparisons can be made between the two groups which should be interpreted with caution. It would be worthwhile to consider whether there is a place in therapy specifically in patients unable to swallow oral medication or unable to tolerate aromatase inhibitors. The expectation that this treatment would be initiated within secondary care and then transferred out to primary care. Consideration needs to take into account the extra cost relating to this.	The Committee considered the small subgroup of women who are unable to tolerate treatment with any aromatase inhibitor, and those unable to swallow oral aromatase inhibitor medication. Please see FAD sections 4.16 and 4.20.
	4	The evidence provided there is a lot of uncertainty to whether or not fulvestrant at the higher dose (500mg) will provide significant improved outcomes (Progression free survival and overall survival)compared to aromatase inhibitors and as there is a significant increased cost it is difficult to justify including it within he present NICE clinical pathway. It should also be noted that it is likely if patients are given the option of either taking an oral tablet or having two injections administered every month, I suspect that the majority of patients would choose an oral tablet, especially as there is no strong evidence to show that there will any greater benefit. Within the subgroups would it be worth considering patients unable to swallow oral tablets and patients who were unable to tolerate aromatase inhibitors due to side effects.	Comments noted.
NHS Professional	1	We support NICE in this decision. Fulvestrant is not a cost effective use of NHS resources.	Comments noted.
	2	This technology is not a cost effective use of NHS resources. The committee concluded that the ICER for fulvestrant in its licensed dose was likely to be at least £35,000 per QALY gained compared with the aromatase inhibitor anastrozole. However, considerable uncertainty remained regarding this estimate. Unit costs of fulvestrant are significantly higher than current standard treatment. The cost of fulvestrant is currently £1,044.82 for the first month, and £522.41 in subsequent months (excluding VAT). This is based on BNF 61 prices for a 250mg prefilled syringe. The manufacturer reports that this pack size will no longer be available after 2012 due to the licensed dose now being 500mg monthly. This may affect costs. This compares to a cost for anastrozole 1mg daily of £74.48 per month.	Comments noted.

Role*	Section	Comment	Response
	3	The relative clinical effectiveness of fulvestrant compared to aromatase inhibitors is uncertain. There are no RCTs directly comparing the licensed dose of fulvestrant (500mg) against aromatase inhibitors (AIs). A network meta-analysis conducted by the manufacturer to allow these comparisons to be made indirectly suggested no significant differences in overall survival between fulvestrant and the AIs anastrozole and letrozole. Fulvestrant 500mg may offer a longer time to progression (TTP) compared to anastrozole however, there was heterogeneity between the studies included and limitations to the statistical methods used which meant that there was a high degree of uncertainty about the reliability of these results. Evidence submitted by the manufacturer does not reflect current UK clinical practice. In the UK, fulvestrant is considered as a third or fourth line treatment after aromatase inhibitor treatment. This use is outside the current marketing authorisation and therefore outside the remit of this technology appraisal. It is therefore unclear where fulvestrant would fit in the care pathway. no head to head RCT against other aromatase inhibs	Comments noted.
	4	The exact number of patients who would be eligible for fulvestrant in its licensed indication is uncertain, but is likely to be small. The manufacturer estimates that 2,200 women would be eligible under the existing license. Clinical advice offered to NICE suggested that most postmenopausal women now receive an aromatase inhibitor as adjuvant hormone therapy for early breast cancer or as first-line treatment if presenting with advanced breast cancer. This limits the use of fulvestrant under its current license. There were limitations to the quality of the evidence: There were no RCTs comparing the licensed dose of fulvestrant against aromatase inhibitors. A network meta-analysis was conducted by the manufacturer to allow these comparisons to be made indirectly, but there were limitations to the methods used, including possible bias from the selection of the trials, heterogeneity between the trials included, and problems with the statistical methods used. These limitations reduce the reliability of the results of these analyses. Fulvestrant does not offer any improvement in overall survival, nor does it meet the criteria for end of life considerations-no extended survival.	Comments noted.

Role*	Section	Comment	Response
NHS Professional	1	We need to remember that patients with ER positive metastatic breast cancer will live longer than other groups of patients. They will run out of options for anti-hormonal therapy and therefore if wanting and requiring further therapy at this point will recieve chemotherapy. So without the availability of faslodex these patients will be offered chemotherapy with attendant costs and side-effects.	The manufacturer confirmed that fulvestrant is licensed 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. The Committee considered that the most likely position of fulvestrant in UK clinical practice would remain as a third or fourth line treatment after aromatase inhibitors and/or an anti-oestrogen therapy. However, on the basis of the manufacturer's confirmation of the licensed position for fulvestrant (section 4.3), the Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal.(FAD - Section 4.4)
	4	What about patients already taking faslodex?	Please refer to section 1.2 of the FAD.
NHS Professional	2	This technology is not a cost effective use of NHS resources. The committee concluded that the ICER for fulvestrant in its licensed dose was likely to be at least £35,000 per QALY gained compared with the aromatase inhibitor anastrozole. However, considerable uncertainty remained regarding this estimate. Unit costs of fulvestrant are significantly higher than current standard treatment. The cost of fulvestrant is currently £1,044.82 for the first month, and £522.41 in subsequent months (excluding VAT). This is based on BNF 61 prices for a 250mg prefilled syringe. The manufacturer reports that this pack size will no longer be available after 2012 due to the licensed dose now being 500mg monthly. This may affect costs. This compares to a cost for anastrozole 1mg daily of £74.48 per month.	Comments noted.

Role*	Section	Comment	Response
	3	The relative clinical effectiveness of fulvestrant compared to aromatase inhibitors is uncertain. There are no RCTs directly comparing the licensed dose of fulvestrant (500mg) against aromatase inhibitors (AIs). A network meta-analysis conducted by the manufacturer to allow these comparisons to be made indirectly suggested no significant differences in overall survival between fulvestrant and the AIs anastrozole and letrozole. Fulvestrant 500mg may offer a longer time to progression (TTP) compared to anastrozole however, there was heterogeneity between the studies included and limitations to the statistical methods used which meant that there was a high degree of uncertainty about the reliability of these results. Evidence submitted by the manufacturer does not reflect current UK clinical practice. In the UK, fulvestrant is considered as a third or fourth line treatment after aromatase inhibitor treatment. This use is outside the current marketing authorisation and therefore outside the remit of this technology appraisal. It is therefore unclear where fulvestrant would fit in the care pathway.	Comments noted.
	4	The exact number of patients who would be eligible for fulvestrant in its licensed indication is uncertain, but is likely to be small. The manufacturer estimates that 2,200 women would be eligible under the existing license. Clinical advice offered to NICE suggested that most postmenopausal women now receive an aromatase inhibitor as adjuvant hormone therapy for early breast cancer or as first-line treatment if presenting with advanced breast cancer. This limits the use of fulvestrant under its current license. There were limitations to the quality of the evidence: There were no RCTs comparing the licensed dose of fulvestrant against aromatase inhibitors. A network meta-analysis was conducted by the manufacturer to allow these comparisons to be made indirectly, but there were limitations to the methods used, including possible bias from the selection of the trials, heterogeneity between the trials included, and problems with the statistical methods used. These limitations reduce the reliability of the results of these analyses. Fulvestrant does not offer any improvement in overall survival, nor does it meet the criteria for end of life considerations.	Comments noted.