AstraZeneca UK Limited · Horizon Place · 600 Capability Green · Luton · LU1 3LU
T: +44 (0) 1582 836000 · F: +44 (0) 1582 83800 · www.astrazeneca.co.uk

Kate Moore
Project Manager
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD
United Kingdom

13th Sep 2011

Dear Kate,

Single Technology Appraisal – Appraisal Consultation Document – Fulvestrant for locally advanced or metastatic breast cancer

Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). Although, AstraZeneca believes the ACD provides a basis for consultation, we strongly contest some of the interpretations and conclusions that led to NICE's draft recommendation.

AstraZeneca remains fully committed to working with NICE and is willing to explore all possible solutions, which would enable fulvestrant 500mg to be available on the NHS as a cost-effective option for patients with advanced breast cancer.

In commenting on the ACD, we have responded to each of the specified questions as follows:

1. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

No. Fulvestrant is a valuable, effective alternative treatment option for suitable 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, as acknowledged by the clinical and patient experts at the Appraisal Committee meeting.

2. **Has all of the relevant evidence been taken into account?**

We can confirm that all relevant clinical evidence has been taken into account. However, AstraZeneca challenges some aspects of the interpretation of the data and understanding of current clinical practice as these have resulting implications for the patient population relevant to this appraisal. Please see below.

3. **Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?**

No. The ERG's summaries of clinical and cost effectiveness were reasonable interpretations of the evidence. The appraisal committee's conclusion, however, appear to be at odds with this. As such, there are a number of areas in the appraisal committee's interpretation of the evidence, which would benefit from clarification or correction. The key aspects include the following (further detail is highlighted in the attached table):

I. The role of tamoxifen in current clinical practice (see comments on Section 4.4 in table below)
II. The likely position of fulvestrant 500mg (see comment on ''Summary of Appraisal's key conclusions: Current Practice'' in table below)
III. Heterogeneity of trials in the network meta-analysis (inclusion/exclusion criteria) (see final three comments in table below)

4. **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?**

   No

5. **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?**

   A NICE approval would help reduce existing inequality in care and regional variations in the availability of funding for fulvestrant.

Please do not hesitate to contact myself or [redacted] ([redacted]) should you require any further information or clarification.

We look forward to the further development of the provisional recommendations and the Final Appraisal Determination.

Kind regards,

[redacted]

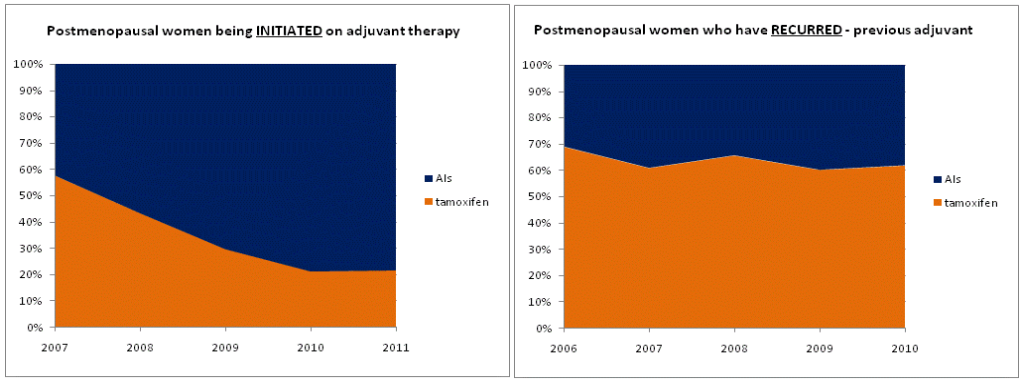
[redacted]

[redacted]

Market Access and Outcomes Research
T: [redacted] | F: [redacted]
E: [redacted]

AstraZeneca Comments

Section	Page	ACD Statement	Comment
3.2.1	13	***'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'***	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.
4.4	21-22	***'.....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'***	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)]
4.4	22	***'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***	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]

Section	Page	ACD Statement	Comment
		inhibitor……'	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.  HMSL data (Cegedim Strategic Data UK) **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 4. NICE CG80: Early and locally advanced breast cancer: diagnosis and treatment (2009)
4.6	23-24	***"Relative to this comparator, the Committee noted that fulvestrant 500 mg offered benefits in increasing the TTP, but that the difference***	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.

Section	Page	ACD Statement	Comment
		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."	
4.7	24	"***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***."	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.
4.9	26	***"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;***	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.

Section	Page	ACD Statement	Comment
		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"	2. 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.
Summary of Appraisal's key conclusions: Current Practice - What is the position of the treatment in the pathway of care for the condition? [relating to ACD section 4.4]	32	***'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.'***	**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. **2. 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.
Summary of Appraisal's key conclusions: Evidence for	32-33	***"…The Committee was also aware that no firm eligibility criteria for trials included in the network meta-analyses***	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

Section	Page	ACD Statement	Comment
clinical effectiveness – Availability, nature and quality of evidence [relating to ACD section 4.9]		***could be produced by the manufacturer"***	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). **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'. 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. *Section 5.7.2.1 (p77-78) of the MS provides the reasoning behind setting 'at least 70% ER+ status' as a criterion.

% 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

Section	Page	ACD statement	Comment
Summary of Appraisal's key conclusions: Evidence for clinical effectiveness – Availability, nature and quality of evidence [relating to ACD section 4.9]	33	***"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"***	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.