National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Fulvestrant for locally advanced or metastatic breast cancer

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, 5 July 2011** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 27, Section 5.3.4	Amendment of first variable for fulvestrant 500mg vs. fulvestrant 250mg from "TTP/PFS for fulvestrant **250**mg" to "TTP/PFS for fulvestrant **500**mg"	Incorrect. To be consistent with the manufacturer's submission, see Section 6.7.7	The manufacturer means Table 35. We have amended this

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 35, Section 5.3.12	Addition of scale value (0.045) for letrozole for TTP/PFS	The TTP/PFS scale value is missing for letrozole, but reported for other comparators listed in the table	The manufacturer means Table 27. We have amended this

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Figure 1. Figure shows that fulvestrant is licensed for third line treatment.	Removal of fulvestrant at third line	Fulvestrant is not licensed in the third line setting. Please see page 24 of MS dated 15th April 11 for the correct diagram.	Figure changed accordingly

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
[redacted]	[redacted]	[redacted]	[redacted]

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Figure 3, Page 23. Lines of previous endocrine therapy for LABC/MBC in the CONFIRM trial	Annotate whether patients are *de novo* advanced or not	Clarity required to avoid confusion when presenting to the appraisal committee. In both the post AO and post AI subgroups it is made clear which population have had adjuvant therapy and then fulvestrant as first line ABC treatment. It is not clear that the other arms are patients that were *de novo* advance patients (presented at diagnosis with ABC) and as such had fulvestrant as second line ABC treatment. The importance of this clarification is that although patients are receiving fulvestrant in different lines of therapy they have both had a similar number of previous therapies.	Re-worded the boxes to denote whether *de novo* ABC or not

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11. In the NHS in England and Wales patients are commonly treated using a 'switch strategy'.	In the NHS in England and Wales patients are sometimes treated using a 'switch strategy'.	Market research has shown that switch strategy is actually declining – please see insert	Changed 'commonly' to 'sometimes'

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 52. Median TTD for Faslodex 250mg –no previous therapy for advanced disease shows 22.2months	Please change to 22.1 months	22.1 months is the figure submitted in the MS	Changed TTP to ’22.1’ The ERG also noted the term ‘AO or AI (mixed population)’ was not strictly speaking accurate in Tables 50 to 53 and this has also been changed The ERG also noted that in the first column of Tables 50 and 51, most of the n values were incorrect – these have been corrected

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Steger study described as single centre study	The Steger study consolidates clinical experience from the ‘Faslodex’ Compassionate Use Programme, including a total of 339 patients treated at eight cancer centres.	Incorrect interpretation of clinical paper	Deleted the words ‘single centre’

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 44 and 45 Faslodex 250mg LD and 250mg	Please add footnote stating none of these dosing regimens are licensed	Fulvestrant is only licensed at 500mg using the loading dose regimen as detailed in the SmPC.	Footnotes added to Table 44 and 45

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
6.1.3 Studies 20/21 are described statistically non-significant	**Please amend** '*The same approach was used for anastrozole and letrozole: this appears fully justified in the case of anastrozole since key clinical trials comparing anastrozole with fulvestrant 250mg, demonstrated very similar (and statistically non-significant) TTP/PFS and OS results*. **To read** '*The same approach was used for anastrozole and letrozole: this appears fully justified in the case of anastrozole since key clinical trials comparing anastrozole with fulvestrant 250mg (which were powered for non-inferiority), demonstrated very similar (and statistically non-significant) TTP/PFS and OS results'*	Incorrect interpretation of clinical papers. Fulvestrant met its primary end point of non-inferiority in these studies.	Wording changed as suggested

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11. In the NHS in England and Wales patients are commonly treated using a 'switch strategy'.	In the NHS in England and Wales patients are sometimes treated using a 'switch strategy'.	Market research has shown that switch strategy is actually declining. Please see insert:  Post menopausal Breast Cancer Hormo	Repetition of issue 6 The ERG believes that this problem refers to pg17 of the ERG report where the statement about the switch strategy on pg11was repeated – the ERG has changed the word 'commonly' to 'sometimes' on both pages

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28, section 4.1.3, first paragraph, second sentence	Text currently states there were 762 patients in CONFIRM – this should read 736	As per CSR	Changed to 736

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35, section 4.1.6, second paragraph, fourth sentence	Text currently states that the CONFIRM 75% survival analysis will be performed when 554 deaths have been observed. This should read 552	75% of 736 patients= 552	Changed to 552

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43, figure 5	Updated forest plot required; current forest plot contains an error	An inconsistency has been noted in the calculation of the visceral involvement covariate of the CONFIRM trial. This has been corrected and regulatory authorities have been notified. This has no impact on the primary analyses of TTP and does not change the conclusions of the secondary analysis of TTP. However the forest plot presented here needs to be updated with the revised one.	Changed as requested  forest plot post errata.doc

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43, second paragraph under figure 5, second sentence.	Text currently states ‘As in CONFIRM, most responses were CR. Only two patients experienced a CR’ This should read ‘As in CONFIRM, most responses were PR. Only two patients experienced a CR’’.	Typo	Changed first ‘CR’ to ‘PR’

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 46 the second paragraph explaining the interpretation of the TTP/PFS network meta-analysis results is not correct. In order to determine which treatments are more efficacious than Faslodex 250mg it is necessary to evaluate both the scale and shape simultaneously. Therefore, to evaluate the 'significance' of the treatment in the way described requires that the shape (or log shape) parameters be equal for all treatments.	**Please delete second paragraph on pg. 46** '*The sign of the difference in scale shown in Table B36 [Table 13] 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. Results shown in Table B36 suggest that Fulvestrant 500mg (and letrozole 0.5mg) result in significantly better TTP/PFS than fulvestrant 250mg whereas Anastrozole 1mg results in significantly worse TTP/PFS than Fulvestrant 250mg. There were no statistically significant differences in TTP/PFS between the remaining treatments compared with fulvestrant 250mg'* **and replace with** *'If the log shape is equal for all treatments, the sign of the difference in scale shown in Table B36 [Table 13] 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*	This error affects the interpretation of the TTP/PFS results. Given that a two-parameter model was used, it is not appropriate to make conclusions regarding the significance of the treatments compared on the basis of one parameter only.	The original paragraph was copied directly from the manufacturer's clarification response. This has now been changed to the suggested new wording.

This same issue arises on Page 48 in the paragraph below Table 17.	*significant (assuming a constant shape)'* **Please delete first paragraph on pg. 48** *'The difference in scale and shape parameters describes the TTP/PFS curves for each intervention relative to the scale and shape parameters of the baseline comparator, fulvestrant 500mg. The curve for fulvestrant 500mg is above all the others indicating that it provides improved TTP/PFS compared to the other treatments. The sign of the difference in scale denotes whether the treatment improves TTP/PFS more than the comparator (if the difference in scale is positive then the treatment is better, if the difference in scale is negative the baseline comparator is better). If both limits of the confidence intervals have the same sign then the difference is statistically significant.'* **and replace with** '*The difference in scale and shape parameters describes the TTP/PFS curves for each intervention relative to the scale and shape parameters of the baseline comparator, fulvestrant 500mg. The curve for fulvestrant 500mg is above all the others indicating that it provides improved median TTP/PFS compared to the other treatments. If the shape parameter is constant across the treatments, the sign of the difference in scale denotes whether the*		Changed accordingly

	treatment improves TTP/PFS more than the comparator (if the difference in scale is positive then the treatment is better, if the difference in scale is negative the baseline comparator is better). If both limits of the confidence intervals have the same sign then the difference is statistically significant, assuming a constant shape.'		

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inconsistency in text on Page 77	Please delete the following sentence from the first paragraph on page 77 *'However, there is no corresponding adjustment made to the OS estimate so the model allows the number of pre-progression patients to exceed the total number of patients alive.'*	The preceding sentence implies that this sentence cannot be true.	Have re-worded this to: 'Without this forced alteration the estimated post-progression survival for both fulvestrant arms would take negative values from year 10 onwards, indicating the essentially incompatible nature of the projective models used for TTP/PFS and OS. There are no inbuilt error-checking mechanisms within the model to detect such anomalies.'