National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **4 September 2013** 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 proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Typing error in the abbreviations list

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 4, the abbreviations list contains a typing error for the full description of ECOG PS	"Easter" should be replaced by "Eastern"	Typing error	Corrected

Issue 2 Redundant word in page 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 14, there is a redundant word in the following sentence: "*Therefore, the population in the AFFIRM study is also likely to BE have more advanced disease and worse treatment outcomes*".	The word "BE" should be removed. The sentence should read "*Therefore, the population in the AFFIRM study is also likely to have more advanced disease and worse treatment outcomes*."	Typing error	Corrected

Issue 3 Implications arising from population differences

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 14, 29 and 83 the ERG state: "*If the subgroup of patients who had received one prior chemotherapy in the COU-AA-301 study is considered to have better treatment outcomes because they have less advanced disease then the total population should have more advanced disease and*	Suggest replacing with: "[...] *Therefore, the population in the AFFIRM study is also likely to have more advanced disease and worse treatment outcomes. While this effect is not accounted for within the submission, the implications of this suggest enzalutamide is effective across the whole trial population while the case made within the NICE appraisal of abiraterone focussed on an easier to treat one prior chemotherapy subgroup"*	The enzalutamide MS intentionally did not account for the fact that the abiraterone data was based on treating an arguably easier to treat population, in order to be conservative and to reduce introducing additional uncertainty by correcting for this. The ERG acknowledge that "*[…] the population in the AFFIRM study is also likely to be have more*	This is not a factual error. No change made.

worse treatment outcomes. Therefore, the population in the AFFIRM study is also likely to be have more advanced disease and worse treatment outcomes. The implications of this in terms of effectiveness of the interventions are unknown." This implication proposed by the ERG contradicts the prior description of the relative effectiveness of enzalutamide and abiraterone.		*advanced disease and worse treatment outcomes."* and it therefore seems unbalanced that the implication does not acknowledge the effectiveness of enzalutamide throughout the whole trial population.	

Issue 4 Representation of Overall Survival data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 15 and 17 the statistical significance of comparative OS gain between enzalutamide and abiraterone is described as follows: "*In contrast, no significant differences were observed for OS or time to first SRE.*" This is factually correct, however we feel that it is relevant to the Appraisal Committee's decision to acknowledge that the difference in OS was on the boundary of statistical significance with a clear	Additional text to qualify the relative gains in OS should be added: Suggest: "*In contrast, no significant differences were observed for OS or time to first SRE, however ,OS was strongly suggested to have improved with enzalutamide: HR: 0.835, 95% CI [0.668; 1.044] showing a benefit which was at the border of significance"*	To more fairly represent key data relevant to the Appraisal Committee's decision.	This is not a factual error. No change made.

numerical advantage for enzalutamide, and confidence intervals which only crossed the significance threshold by 4%			

Issue 5 Typing error regarding tolerability in AFFIRM and COU-AA-301

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In pages 16 and 81, it is mentioned that the percentage of patients who discontinued treatment due to an AE was higher with intervention drug than with placebo in AFFIRM and COU-AA-301. This is incorrect.	Suggest rewriting as: "*In both studies, the proportion of patients who discontinued treatment due to an AE was LOWER with study intervention (enzalutamide and abiraterone) than the comparator*"	The information is incorrect	Corrected. The same mistake was made in the MS, on page 105.

Issue 6 Wrong MS pages cited

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 18, it is stated that Tables 83 & 84 are located on MS pages 183-184, however, they are located on pages 181-182	Suggest rewriting as: "*MS: Table 83 & Table 84; p. 181-182*"	Wrong page numbers from the MS	Corrected

Issue 7 Price disclosure

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 18, the ERG report states "[redacted]	Mark as CIC	To avoid implying the enzalutamide PAS discount	Now marked CiC (blue)

Issue 8 Incorrect intervention

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 20, it is stated that the systematic literature review was conducted to determine effectiveness of *"abiraterone"* however, it should read "*enzalutamide*"	Suggest rewriting as: "*A thorough systematic review was completed looking for evidence that might allow a network meta-analysis to be conducted to determine the effectiveness of ENZALUTAMIDE relative to the designated comparators.*"	The systematic literature review was conducted to identify studies that would allow a network meta-analysis to assess effectiveness of enzalutamide and not abiraterone	Corrected.

Issue 9 Number of patients with EQ5D in AFFIRM

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 57 and 103, within the section regarding EQ-5D, it is stated: "*Incidentally, the EQ-5D numbers presented in chapter 6.5.3.3 of the MS (MS, Table 17, page 68)*[13] *are not consistent with*	Suggest removing this sentence, as Table 17 relates to AFFIRM whereas section 7.4.6. provides EQ-5D data from studies other than AFFIRM.	The two sections provide different numbers because they relate to different studies. Enzalutamide-related EQ-5D data are not provided in section 7.4.6.	We are referring to the numbers on page 146 (section 7.4.6). According to the text these numbers relate to the AFFIRM trial and they are not consistent with the data in table

the data reported in chapter 7.4.6 of the MS (MS, page 146)" This is incorrect.			17. No change made.

Issue 10 Typing error in the Fizazi 2012 reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 74 and 75 (legends of Tables 4.19 and 4.20) the reference Fizazi 2011 should be Fizazi 2012	Replace Fizazi 2011 with Fizazi 2012 in the legend of table 4.19	Fizazi et al was published in 2012. This typing error was also in the MS	Corrected

Issue 11 OS for the control arm of COU-AA-301

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In table 4.25 (page 85), median OS for PP in COU-AA-301 is stated as 11.7 months. Reference to the ERG report for abiraterone should be stated, as median OS for the PP arm in the final analysis (Fizazi) was 11.2 months	Median OS for PP (COU-AA-301) in Table 4.25 should be cross-linked to the ERG report for abiraterone	Given that the final OS for PP reported in Fizazi 2012 is lower, the reader may get confused unless cross-reference to the abiraterone ERG report is added	Reference added.

Issue 12 Cross-referenced to the wrong MS section

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 94, section 5.2.3. should be cross-referenced to the MS section 7.2.1. on page 120	Suggest replacing "*MS, pg. 120, section 6.3.3*" with "*MS, pg. 120, section 7.2.1*".	Incorrect cross-reference	Corrected

Issue 13 Cross-referenced page for Figure 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 100, the legend of Figure 5.4. includes a mistyped source which reads "*Source: MS, Figure 19, pg. 127*."	Suggest replacing with "*MS, Figure 19, pg. 128.*"	Incorrect page number	Corrected

Issue 14 Incorrect source for Table 5.10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 110, the source of Table 5.10, reads: "*Source: Response to the Clarification Letter, Tables 86- 87, pg. 186.2*." However, the tables are from the MS	The source for the Tables is the MS	Incorrect source	Corrected to: "*Source: MS, Tables 86- 87, pg. 186.13*"

Issue 15 Incorrect Table numbers in page 112

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 112, section 5.2.10, the table numbers which are cross-referenced are not correct.	Suggest replacing with: "*Multiple sensitivity analyses were performed, the 10 most influential sensitivity analyses (based on the 95% confidence intervals of the input parameters) for both comparisons are presented in Tables 5.12 and 5.13 (sorted by ICER spread)*"	Incorrect cross-reference	Corrected

Issue 16 Source of Table 5.14 is incomplete

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 115, table 5.14, the source includes tables from the response of the clarification letter and the MS	Suggest replacing with: "*Source: Response to the Clarification Letter, A2.1- A2.43,2 and MS, Tables 86 -87.*"	The tables correspond to two files	Corrected

Issue 17 Source for Table 5.15 is incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 116, source of Table 5.15 is stated as "*MS, Table 72, pg. 173."*	Suggest replacing with: *"Source: MS, Table 71, pg. 173"*	The table number is incorrect	Corrected

Issue 18 CIC and AIC data not underlined

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the ERG report, CIC and AIC data is highlighted, but not underlined.	CIC and AIC data should be underlined and highlighted.	Prevent accidental disclosure of in confidence data.	Corrected

Issue 19 Typing error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 102, the ERG refers to the "*COU-AA-310*" trial	The trial should be written "*COU-AA-301*"	Typing error	Corrected.

Issue 20 Incorrect patient numbers for baseline EQ-5D

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 103 and 122 the ERG report state: "*At baseline 126 of 800 [16%] patients in the enzalutamide arm and 53 of 399 (13%) patients in the placebo arm completed the EQ-5D (MS, Table 17, pg. 68).*" These figures are incorrect baseline values	Suggest replacing with: "*At baseline 142 of 800 [18%] patients in the enzalutamide arm and 67 of 399 (17%) patients in the placebo arm completed the EQ-5D (MS, pg. 146).*"	Table 17 in the MS refers to the number of patients with a baseline and at least 1 post-baseline EQ-5D. The correct number of patients who completed the EQ-5D at baseline is described in section 7.4.3 in the MS.	Corrected.

Issue 21 Speculative text on AFFIRM population severity

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 103 states: "*Together with the fact that the population in the AFFIRM trial could have been fitter than generally seen in clinical practice, the utility value of* [redacted] *could be an overestimation of the quality of life of the patient population.*"	Suggest that this text is removed.	The possibility of AFFIRM patients being fitter than those generally seen in clinical practice is presented as a fact, however, this is not substantiated within the ERG report. In fact, in section 3.1, p. 29. the ERG argues the contrary as:	The ERG recognizes the fact that the text "*Together with the fact that the population in the AFFIRM trial could have been fitter than generally seen in clinical practice"* was not substantiated with evidence in the report. However, the

This is not a fact and not substantiated anywhere in the ERG report. The same section is repeated on p. 122 and p. 124		• In the NICE guidance for abiraterone the committee considered patients who had received one prior chemotherapy in the COU-AA-301 trial • The Committee noted that this subgroup (...) probably reflected the population in England and Wales for whom abiraterone would be considered • "*If the subgroup of patients who had received one prior chemotherapy in the COU-AA-301 study is considered to have better treatment outcomes because they have less advanced disease; then the total population should have more advanced disease and worse treatment outcomes. Therefore, the population in the AFFIRM study is also likely to be have more advanced disease and worse treatment outcomes."* Following the logic of the ERG, the utility value of [redacted] could actually be an <u>under</u>estimation of the quality of life of the patient population.	second part of the sentence also relates to the text before this sentence: "*However, the ERG does regard the EQ-5D utility value as uncertain for the following reasons. Only a very small proportion of the patients in the AFFIRM trial completed/were asked to complete the EQ-5D: At baseline 142 of 800 (18%) patients in the enzalutamide arm and 67 of 399 (17%) patients in the placebo arm completed the EQ-5D (MS, pg. 146). In addition, the proportion of patients with missing items among those asked is considerable (response 60-64%)*." In the ERG's opinion it is possible that the utility value of [redacted] is an overestimation of the quality of life of the population in question in practice for those reasons. The text was changed as follows: *"The patients in AFFIRM who responded could have been fitter than patients generally seen in clinical practice. Therefore, the utility value of [redacted] could be an*

			overestimation of the quality of life of the patient population."

Issue 22 Incorrect statement on lack of information on utility increments

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 104, the ERG states "In the response to the clarification letter (Response to the Clarification Letter, pg. 18) the manufacturer has repeated the same arguments and information as stated in the MS and did not provide the details on the calculation of the utility increments for on treatment benefits." The same argument is repeated on p. 125	Suggest that this text should be removed	The requested information was provided in the manufacturer's response to the ERG clarification letter, question B4.b, including the SAS procedures used, the covariates of the model, and the outcomes. As described in the response, the utility increments were calculated as the difference between the LSMEANS.	The text was changed as follows: "In the response to the clarification letter (Response to the Clarification Letter, pg. 18) the manufacturer provided the details on the calculation of the utility increments for on treatment benefits. However, the covariates table was still missing"

Issue 23 Incomplete argument on low patient numbers to calculate baseline utility

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 103, the ERG argues that the utility values are uncertain due to low patient numbers. This statement lacks a reference to the FACT-P mapped baseline utility, available from 1,009 patients and supporting the EQ-5D value.	Suggest that this text should be removed	By only providing the patient numbers for the EQ-5D and not referencing the supporting FACT-P data, the ERG exaggerates the uncertainty surrounding the baseline utility.	Not a factual error. No change made. The ERG refers specifically to the EQ-5D utility value. Moreover, the Manufacturer considers the mapped baseline utility values based on FACT-P responses as uncertain and

			uses the collected EQ-5D responses.

Issue 24 Incorrect reference to model parameter

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 112 states: "For enzalutamide compared to abiraterone, the HR used to calculate OS for abiraterone was considered the most influential variable resulting in an ICER spread ranging from £11,843 to £46,022. [...] As noted by the Manufacturer, the impact of these HRs and other correlated parameters included in the sensitivity analyses is actually smaller than presented in Tables 5.12 and 5.13" This is incorrect, and repeated on p. 126, lines 6 and 7.	The text should be modified to: "For enzalutamide compared to abiraterone, the time covariate from the linear vs. time model to calculate the abiraterone OS HR was considered the most influential variable resulting in an ICER spread ranging from £11,843 to £46,022.[...] As noted by the Manufacturer, the impact of correlated parameters (such as the intercept and time covariate of the abiraterone time dependent HR) included in the sensitivity analyses is actually smaller than presented in Tables 5.12 and 5.13"	The HR is derived from two parameters: an intercept and a time covariate. In this analysis only one parameter was varied at a time without varying the other (correlated) parameter.	Not a factual error. No change made. Although the description of the manufacturer contains more details, the quoted section from the report did not contain a factual error (e.g. it was not stated that a constant HR was used) and these details were described elsewhere in the report. Therefore, no change was made.

Issue 25 Uncertainty in OS estimate

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 130, the ERG states: "*However, based on the economic model, it can be estimated that enzalutamide has 2.88 months survival benefit over best supportive care. The model provides an indication of mean life years ("Life Years cumulative" on the "Calculation..." sheets).* *Assuming that the duration of the AFFIRM trial was 24 months, the modelled values are as in the table below (the closest approximation is 2.01 years).*" This is not the most appropriate way to estimate the survival benefit of enzalutamide	Suggest removing both the text and Table 7.2	The estimated OS gain truncated at 24 months is misleading and irrelevant. In other appraisals in the same indication (abiraterone: TA259, cabazitaxel: TA255), the committee considered the OS gain estimated in the base case economic analysis as sufficient evidence for the > 3 months extended life criterion. Enzalutamide showed an OS gain of [redacted] in the economic model. Also the gain in median OS is more than 3 months.	Not a factual error. No change made.