NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen [ID600]

Dear [redacted]

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have now had an opportunity to take a look at the submission received on 26 June 2013 by Astellas Pharma. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **29 July 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Ahmed Elsada, Technical Lead (ahmed.elsada@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1. **Study selection**

a. According to the flow diagram on page 38, 3235 records have been screened and 3055 records have been excluded, leaving 51 full-text articles to be assessed for eligibility. However, after excluding 3055 from 3235 the remainder is 180. Please provide a corrected flow diagram or a justification for not including all of the 180 records in the flow diagram. Please also explain the difference between the last two boxes in the flow diagram on page 75 (that is, from 131 records included in the qualitative synthesis to 9 records included in the quantitative synthesis).

b. The flow diagram on page 38 indicates that 5 studies were included in the qualitative synthesis. Please clarify if this refers to 5 studies or 5 publications describing 1 study? On page 39 (first two bullet points), 5 publications are listed; please clarify if this should be 5 'studies'?

c. Reference 36 (De Bono, 2012) is described in the submission as a published article but provided in the reference pack as an ASCO abstract. Please clarify whether it is a published article or an abstract, and if the former, please provide the article.

d. According to the eligibility criteria in table 5 (page 36), studies of enzalutamide, abiraterone (plus prednisone or prednisolone) and mitoxantrone (plus prednisone or prednisolone) were eligible for inclusion in the systematic review. However, only studies of enzalutamide were included. Please justify why studies of other interventions were excluded.

A2. **Priority Question:** Table 20 (page 79) does not provide details on best supportive care. Please provide details on what constituted best supportive care for both trials.

A3. **Priority Question:** The clinical study report does not provide UK-specific data. Please provide UK data for the AFFIRM study.

A4. **Priority Question:** The rationale for excluding mitoxantrone from the decision problem is given on page 34 as:

'Mitoxantrone is not licensed for mCRPC nor is it listed in NICE clinical guidelines as a treatment option for mCRPC, hence it was agreed with NICE during the 'Section A meeting' that mitoxantrone would not be considered a relevant comparator in the current decision problem.'

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According to NICE, at the Decision Problem meeting '*The manufacturer laid out the reasons for why they do not consider mitoxantrone a comparator, and we said that this was not unreasonable, and that they have to provide this justification including information from use in clinical practice in the submission*.'

Please provide a justification for excluding mitoxantrone as a comparator (with references wherever possible), taking into account that the absence of a UK licence or the fact that it is not in NICE guidance is not a sufficient reason to exclude a treatment as a comparator if it is routinely used in UK clinical practice. Please see the 2013 NICE methods guide, sections 6.2.1 to 6.2.4 on selecting comparator technologies for further information.

A5. Please present estimates of mean overall survival, by treatment group, with the analysis truncated at 5 years for each parametric distribution used (exponential, Weibull, log-logisitc, log-normal and gamma).

A6. The placebo arms in the COU-AA-301 (in which all patients received prednisone) and AFFIRM trials were assumed to have the same treatment outcomes for the purpose of the indirect comparison on the basis that 'there is no evidence to suggest that steroids have an impact on PFS or OS' (section 6.7.7, page 87). Please justify why steroids have no impact on patient reported outcomes such as pain, quality of life and adverse events.

A7. In table 24, page 83, the two studies show significant differences for disease location: 'Node' (enzalutamide 11.6%, placebo 8.5%; abiraterone 45%, placebo: 41%), and 'Liver' (enzalutamide 55.8%, placebo 55%; abiraterone 11%, placebo 8%). However, in the Supplementary Appendix from Scher 2012 (NEJM), page 15, the data for the AFFIRM study are the other way round. Please clarify which of these are the correct data.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** On page 126 it is stated that: '*Experts (70) evaluated the plausibility of the slope and the curves' tail, and the proportion alive at 2 and 3 years. The Weibull distribution was chosen over the Log-Logistic distribution to model OS due to the more realistic shape of the 'tail*". A similar justification is provided for choosing the Weibull function over other parametric functions to model progression-free survival; on page 129 it is stated that: '*Log-Logistic model has the best statistical fit according to AIC and BIC criteria. However, the Weibull model was selected after validation by clinical experts due to the more realistic shape of the tail*'.

a. Please provide a more detailed justification as to why, for OS and PFS, the tails of the Weibull curves were considered more realistic than the log-logistic curves (pages 126 and 129) which fit the data best according to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

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b. Please provide the probabilistic outcomes (both mean outcomes as well as incremental outcomes) using the Weibull function instead of the log-logistic models for progression free survival (PFS) and overall survival (OS), as suggested by AIC and BIC.

B2. **Priority Question:** The hazard ratio (HR) applied to the parametric function to estimate overall survival after treatment with abiraterone is not based on the final results of the COU-AA-301 trial (as published by Fizazi et al. 2012). Instead, it is argued that the proportional hazard requirement was not met, and thus a time-dependent HR should be adopted (Appendix 14, page 243-244). The selected HR, increases to 1.39 at 25 months indicating a worse survival probability (probability per cycle) for abiraterone than for best supportive care. This HR is kept constant at 1.39 after 25 months.

a. Please justify the choice of the HR; specifically, why was the HR presented on page 127 considered the best fit based on visual inspection, and why was the published (constant) HR of 0.74 not selected for the base-case analysis?

b. Please justify the assumption to keep the HR at 1.39 after 25 months, and provide a sensitivity analysis which demonstrates the effect on the ICER of assuming instead that the HR is 1.0 (as there are no data after this time point in the paper published by Fizazi et al. 2012).

c. Please provide the probabilistic outcomes (both mean outcomes as well as incremental outcomes) using all different HRs presented in Appendix 15; four piecewise HRs, three linear versus time HRs and the constant HR of 0.74 as reported by Fizazi et al. (2012).

B3. **Priority Question:** The utility values for on-treatment benefits for both enzalutamide ([redacted]) and abiraterone (0.04) were based on mapped FACT-P utilities.

a. Please provide a summary of the mean values, number of observations and dispersion (standard deviation) for the EQ-5D and FACT-P elements, stratified by being on-treatment, and by treatment group (for enzalutamide and best supportive care from the AFFIRM trial as well as for abiraterone and best supportive care from the COU-AA-301 trial).

b. Please also provide the algorithm used to calculate the utility increments, and please describe how the utility increments were calculated based on the information provided in response to B3.

B4. **Priority Question:** According to the NICE Methods Guide, probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models. However, only the deterministic results are provided in the submission.

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Please provide the probabilistic outcomes (both mean outcomes as well as incremental outcomes) for all analyses presented in the results section (sections 7.7.1–7.7.9).

B5. Utility loss associated with pain is included in the model by applying a utility decrement for the adverse events (AEs) and serious reportable events (SREs), and by using the 'on-treatment' utility gain, which introduces double counting (since utility benefits of enzalutamide and abiraterone were already included in the model). On page 189, it is stated that '*the model is relatively insensitive to the utility decrement for AEs and SREs*' and thereby arguing that the '*double counting in utility values is not likely to have a big impact on the incremental cost effectiveness results*'. However, the scenario analysis (section 7.7.69, table 88) were double counting was prevented (analysis 13) resulted in a higher ICER (£51,343 per QALY gained). Please provide detailed justification as to why the 'on-treatment benefit' for enzalutamide (expressed as a utility increment) was considered in addition to the disutility associated with AEs and SREs.

B6. The disutility for progressive disease was calculated as -0.085 based on Sandblom et al. (2004). Section 7.4.7 (page 152) states that: '*the utility decrement derived from the Sandblom study (-0.085) was considered the most appropriate value, as the collected time intervals (16-8 and 8-0 months before death) approximately match the time in stable and progressive disease for AFFIRM patients*', which assumes that the decrease in utility from 16-8 months before death to 8-0 months before death represents the utility decrement for progression (page 154). However, these time intervals should match the time in stable and progressive disease states for patients in Sandblom et al. and not AFFIRM because in this calculation it is assumed that patients for whom the utility values are measured have progressive disease 8-0 months before death and are stable 16-8 months before death. Also, it is likely that some patients will still be progression free 8-0 months before death (for example, patients who die due to other causes than cancer) while others may have already progressed 16-8 months before death. Please provide a detailed justification as to why the disutility of -0.085 was taken from the Sandblom et al. study to estimate the utility for progressed patients, taking into account these comments.

B7. In table 59 (page 154) the reference for on-treatment benefit for abiraterone is given as '*Abiraterone CVZ submission (CFH rapport 12/01: abiraterone -Zytiga. Feb 2012)*'. This report is not in English. Please provide the reference of the original source.

Section C: Clarification on Search Methods

C1. Please clarify which database hosts were used for all searches, e.g. Embase (OvidSP).

C2. Please provide strategies and host for the Medline In-Process searches.

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C3. Please explain why you searched PubMed and Medline.

C4. Please clarify whether a published/verified study design filter was used in the searches in tables 94, 95 and 96 in section 10.2.4. If a validated study design filter was used, please provide a full reference to the filter.

C5. Please give the exact date span for the databases used in all searches, e.g. Medline (OvidSP): 1946-2013/07/09

C6. Some of the line combinations in table 97 in section 10.2.4 are incorrect. The search strategy consists of 23 lines; however, in line 20 #42, #43, #44 and #45 have been combined. Please provide a strategy with correct combinations.

C7. The line numbering and some of the line combinations in table 103 are incorrect. The line numbering starts after the search term 'Prostatic Neoplasms'[MeSH Terms]' resulting in line combinations like '14: #5 AND #14'. Please provide a strategy with correct line numbering and combinations.

C8. Please provide more detail about the information gained through 'Google and other search engines', such as the names of the other search engines and search terms used to retrieve results.

C9. Please clarify whether published quality of life filters were used in tables 97, 98 and 99 in section 10.2.4. If a validated study design filter was used, please provide a full reference to the filter.

C10. Please clarify whether published economic filters were used in tables 102, 103 and 104 in section 10.10.4. If a validated study design filter was used, please provide a full reference to the filter.

C11. Please provide the search strategies and web addresses for all conference searches undertaken.

C12. Please clarify which host you used for the Cochrane searches. It does not look like the search syntax by Wiley (Cochrane Library) which is usually used.

C13. Please clarify if Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) were included in the Cochrane database searches.