NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Enzalutamide for the treatment of adult men with asymptomatic or mildly symptomatic metastatic hormone relapsed prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated

Dear [redacted]

The Evidence Review Group, Aberdeen HTA group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 5 February by Astellas. 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 the end of **12 March 2015**. 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 Mary Hughes, Technical Lead (Mary.Hughes@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

Dr Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **PRIORITY** Please clarify how the hazard ratios for overall survival (OS) presented in Table 32 (page 109) were calculated for 'IPCW ENZA vs ABI IA3' and 'IPCW ENZA vs ABI Final'.

A2. **PRIORITY** In Table B35 the relative risks (RR) presented do not appear to match the data. For example, for fatigue 310/871 in ENZA versus 218/844 in Placebo gives RR = 1.38 not the 0.57 presented. The percentage occurrence is higher for all adverse events (AEs) in the enzalutamide group than placebo, yet all the RRs are < 1 indicating less likely. Please check the calculations of RR and 95% CI and present the correct results.

A3. **PRIORITY** Please present additional post-hoc sub-group analyses as follows:

A. Split by steroid use at baseline for OS and for radiographic progression-free survival (rPFS) data from PREVAIL; that is, the equivalent data presented for the steroid use sub-group as for the sub-groups in figures B4 and B6 of the submission.

B. For rPFS please present this separately for the rPFS primary analysis from central review definition and for the rPFS definition used for the comparison with abiraterone.

A4. **PRIORITY** Please provide the corollary of table B18: Time to initiation of cytotoxic chemotherapy for the 30 June 2014 data cut which has not been presented. Similarly, please provide the corollary of cells B8:E25 of the *Second_line_treatment* worksheet of the electronic model for the 30 June 2014 data cut.

A5. **PRIORITY** It is unclear whether tables B59 and B60 relate to the interim data cut (16 September 2013) or the final data cut (30 June 2014). Please clarify this, and present the corollaries of tables B59 and B60 for the data cut which has not been presented, coupled with three estimates of treatment emergent periods these relate to.

A6. Please clarify whether patients in PREVAIL could remain on the study drug but also move onto, and concurrently receive, another anti-neoplastic drug (cytotoxic, hormonal and investigative treatments). If this was possible, for each arm of PREVAIL please present the number of patients this applied to for cytotoxic, hormonal and investigative treatments separately.

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A7. Table B14 shows that 9 patients in the enzalutamide arm of the study received enzalutamide as a subsequent treatment. Please clarify if these patients had started first-line treatment with enzalutamide to which they were allocated.

A8. Please clarify if the indirect comparison reported in Table B33 uses the standard Bucher method for adjustment and utilised data from Table B31.

A9. Please provide further details on the definitions of 'investigator assessed rPFS' and 'independent central blinded review of rPFS' in PREVAIL. Did each assessment use common protocols? If so, please provide details.

A10. In the network meta-analysis, investigator rPFS was used instead of the independent central blinded assessed rPFS. The only rationale for this seems to be: "Given that the analysis of the investigator assessed rPFS includes a higher number of events (N=889), this is the analysis used in the economic model." Please clarify the rationale for using investigator rPFS in the network meta-analysis and why a higher number of events made the outcome more useful for the economic analysis.

A11. The submission states that for TTD curves "*Proportionality of hazards, as assessed by loglog plots, was not met*". The data justifying this does not appear to have been presented. Please provide either the data summary underlying this assertion, or a more explicit reference to this within the references of the submission.

A12. A. Please present the patient distribution in terms of patient numbers by week, split by arm for the data underlying the 43.9 day estimate of the mean time to initiation of cytotoxic chemotherapy after study drug treatment discontinuation.

B. Please confirm which data cut was used to calculate the 43.9 day estimate and present the corollary of this data for the data cut which has not been presented.

C. Please also present the corollary of this data for initiation of antineoplastic therapy.

To be concise, weeks after treatment discontinuation have been requested, but if the corollary of days after treatment discontinuation is simpler to present within an excel spreadsheet this is equally acceptable.

Weeks after Tx disc.	<0	0 (0-7 days)	1	2	3	Etc.
Time to initiation of cytotoxic chemotherapy: interim data cut						
Enzalutamide (N)	n=???	n=???	n=???	n=???	n=???	n=???
BSC (N)	n=???	n=???	n=???	n=???	n=???	n=???

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Time to initiation of cytotoxic chemotherapy: final data cut						
Enzalutamide (N)	n=???	n=???	n=???	n=???	n=???	n=???
BSC (N)	n=???	n=???	n=???	n=???	n=???	n=???
Time to initiation of antineoplastic therapy: interim data cut						
Enzalutamide (N)	n=???	n=???	n=???	n=???	n=???	n=???
BSC (N)	n=???	n=???	n=???	n=???	n=???	n=???
Time to initiation of antineoplastic therapy: final data cut						
Enzalutamide (N)	n=???	n=???	n=???	n=???	n=???	n=???
BSC (N)	n=???	n=???	n=???	n=???	n=???	n=???

A13. Please clarify:

A. What events were treated as events and what were treated as censoring events within the Kaplan Meier curves that underlie the rPFS curves of the electronic model.

B. What events were treated as events and what were treated as censoring events within the Kaplan Meier curves that underlie the TTD curves of the electronic model.

Section B: Clarification on cost-effectiveness data

Quality of life

B1. **PRIORITY** Please submit the full utility report underlying the values of table B64. As a minimum, or if a utility report is not available:

A. Please provide a full set of coefficients for the predictors that were examined coupled with confidence intervals. These data should be presented for all the model forms that were explored and not just for the model form (mixed-effects model for repeated measures) that underlies the values of table B64, coupled with goodness of fit statistics suitable for distinguishing between the models.

B. Please also provide summary statistics by arm for all the predictors examined within the various models.

C. Please also provide an outline of the arithmetic that underlies the central estimates of table B64: for example the sumproduct of the mean values of the predictors and their coefficients.

What was the rationale for preferring the model form (mixed-effects model for repeated measures) that underlies the values of table B64 over the other models that were explored?

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B2. **PRIORITY** Please submit the full utility report underlying the values of table B65 and explanations of the values within it on the same basis as question B1 above concerning table B64.

B3. Please provide Appendices I, II and III from reference 53 (Quintiles report for the analysis of PRO data collected in the PREVAIL study).

B4. Please clarify if within section 7.4.3 remaining on treatment is synonymous with Stable Disease (1st paragraph page 170).

B5. What were the mean (s.d.) quality of life values that were used for TA316 (ref 32) for baseline, treatment effects change from baseline and disease progression? Please confirm that a parallel approach to the TA316 calculation of the quality of life impact of disease progression could not be calculated due to a lack of data within PREVAIL.

B6. What were the mean (s.d.) QALY decrements, or QoL decrements coupled with their assumed durations, that were applied for each SRE within TA316? Please clarify why decrements for SREs based upon a trajectory adjusted mean change as in TA316 were not calculated or not calculable from the PREVAIL EQ-5D data?

B7. Please provide non-redacted tables 46, 49 and 51 of the TA316 enzalutamide post docetaxel company submission, ref 32 (table 46: maximum likelihood parameter estimates for AFFIRM placebo overall survival; table 49: maximum likelihood parameter estimates for AFFIRM placebo time to treatment discontinuation; table 51: number of events and rates for SREs used in the model).

B8. Please confirm whether the functions of tables 46 and 49 of the TA316 enzalutamide post docetaxel submission, ref 32 apply to time measured in months or some other time span, the implied means for OS and TTD for placebo, and, the implied means for OS and TTD for enzalutamide and abiraterone given the estimated hazard ratios

Model inputs and structure

B9. The modelling contains a large number of possible scenarios in terms of the OS curves that can be applied. There is no easy read across between these and the clinical effectiveness tables in the submission and extrapolation report (81_Extrapolation report_Appendix A_14JAN2015.pdf). Please provide table

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references from both the written submission and the extrapolation report, as available, for the parameters underlying the curves referred to in the *Overall_Survival* worksheet cells M100:M114 for enzalutamide, cells M119:M130 for BSC and cells M135:M138 for abiraterone.

	Submission clinical effectiveness section		Extrapolation report	
Cell	Table	Page	Table	Page
M100	???	???	???	???
M101	???	???	???	???
Etc.	???	???	???	???

B10. The modelling contains a large number of possible scenarios in terms of the PFS curves that can be applied. There is no easy read across between these and the clinical effectiveness tables in the submission and extrapolation report (81_Extrapolation report_Appendix A_14JAN2015.pdf). Please provide table references from both the written submission and the extrapolation report, as available, for the parameters underlying the curves referred to in the *PFS* worksheet cells M102:M111 for enzalutamide, cells M114:M120 for BSC and cells M124:M128 for abiraterone.

	Submission clinical effectiveness section		Extrapolation report	
Cell	Table	Page	Table	Page
M102	???	???	???	???
M103	???	???	???	???
Etc.	???	???	???	???