NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy [ID503]

Dear Jennifer,

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 the 16 January 2014 by Janssen. 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 **20 February 2014**. 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

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. **Priority Question**: Please provide the *mean* survival in the BSC group in COU-AA-302 for the overall population and for the subgroup of patients from UK centres.

A2. **Priority Question**: Please provide the *mean survival gain* of abiraterone (AAP) compared with BSC (PP) in COU-AA-302 for the overall population and for the subgroup of patients from UK centres.

A3. **Priority Question**: Please provide the following data for the subgroup of people who received docetaxel following AAP or PP in each treatment arm respectively:

- rPFS results as reported in table 19
- OS results as reported in table 20
- Iterative parameter estimate and Rank preserving failure model HRs as reported in table 22.
- Time on docetaxel treatment

A4. Please provide references for all studies listed in Figure 2. For each reference please provide:

- the line of treatment in which AA, docetaxel or prednisone was taken
- the performance status or severity of symptoms of the trial population

Please provide the text which is hidden in the text boxes in Figure 2.

A5. Please provide a full data extraction of the 32 RCTs included under post-ADT, pre-chemotherapy in Figure 2 that included docetaxel. This should include data on the population, intervention, comparators and primary outcomes. Please state whether each study is relevant to the decision problem and if not the reasons that the study is not relevant.

A6. Please explain why *radiographically assessed* progression-free survival (rPFS) was chosen as a primary outcome in this trial and not another definition of progression such as the disease state progression outcomes which were secondary outcome measures in COU-AA-302 (time to opiate use for cancer pain; time to initiation of cytotoxic chemotherapy, time to PSA progression or time to deterioration in ECOG PS). Please discuss any other measures of progression used in clinical trials for treatments for metastatic castrate resistant prostate cancer that were not used in COU-AA-302, and the reason why they were not measured in COU-AA-302.

A7. The methods for iterative parameter estimate (IPE) and rank preserving failure time model (RPFT) reported in table 22 are not included in the methods section. Please provide a description of this methodology.

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A8. Please provide an estimate of the number of patients who currently may receive docetaxel in UK clinical practice whose symptoms meet the following criteria:

- BPI-SF question # 3 score of 0-3
- ECOG PS grade 0-1
- PSA progression following discontinuation of antiandrogen treatment (using the definition of PSA progression used in COU-AA-302)

A9. Section 6.3.3 describes the patient population in the COU-AA-302 study. Is the population who were eligible to participate in COU-AA-302 mutually exclusive from the population who could receive docetaxel in clinical practice?

- If yes, please state which of the eligibility criteria would exclude patients who may receive docetaxel in routine UK clinical practice from participating in COU-AA-302.
- If no, please state the number of patients included in COU-AA-302 for whom docetaxel may have been considered suitable in routine UK practice

A10. The 3rd interim analysis was after unblinding. Please explain the potential consequences of unblinding for the primary outcomes, reporting of adverse events, treatment discontinuations and all secondary outcomes.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: **HRQoL- post docetaxel treatment**

Page 113 of the MS states that "*The post-docetaxel utility increment of 0.046 (derived from COU-AA-301 trial data) was not applied since the majority of patients were assumed to already have been receiving AAP in this setting. Hence, it was assumed this utility gain was captured in the UK mCRPC Utility Study and to apply it, would be double-counting. These assumptions were explored in sensitivity analyses".* This is inconsistent with the modelling in TA259, as in that submission an on treatment utility gain was applied to the Abiraterone comparator. Also, the sensitivity analysis referred to in the quoted text is not reported in the methods section (Table 62), nor in the results (Table 73).

a. Please provide a description of the treatments received by the people in the mCRPC utility study post ADT.
b. Please explain why the fact that the majority of patients in the UK mCRPC Utility Study were assumed to have already been receiving AAP prohibited the use of differential utility scores for AAP vs BSC in the post-docetaxel phase.
c. Please provide the results of a scenario using the value resulting from the UK mCRPC Utility Study as the utility for patients receiving AAP and subtract the 0.046 for patients receiving BSC in the model

B2 **Priority Question: utility value estimates post docetaxel**

In TA259 the utility value at baseline at which time patients had received docetaxel was based on FACT-P data from COU-AA-301. This utility value is higher than the utility value

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estimated from the UK mCRPC utility study for the post docetaxel treatment phase in the current submission. Please provide the reason for this difference.

B3 **Priority Question: HRQoL- utility increment on abiraterone**.

The concept of the on-treatment utility increment in favour of Abiraterone seems questionable as it is clear that AAP leads to significantly more adverse events (both overall and grade 3&4) than BSC. The submission states that the utility increment assigned to patients in the AAP was to capture *"patient benefits experienced on AAP compared with BSC (PP) with respect to pain and fatigue"* (MS P. 94) but the impact of other adverse events on HRQoL were not considered. Although it is possible that patients have a higher HRQoL during treatment with AAP, in spite of experiencing more adverse events, the choice of not incorporating the impact of adverse events on HRQoL is not sufficiently justified. In addition, it appears as if the effect of varying rates of grade 3/4 AEs is only taken into account in the costs in the docetaxel phase. So, the AE difference between AAP and BSC (PP) is not accounted for, in either HRQoL, or in costs.

Therefore:

a. Please demonstrate how the utility increment for abiraterone reflects the benefits experienced on abiraterone compared to BSC with respect to pain and fatigue in COU-AA-302
b. Please provide the observed FACT-P scores from COU-AA-302 equivalent to all treatment phases in the model, per treatment, for the ITT population.
c. Please provide utility decrements (FACT-P and/or EQ-5D) for all AEs separately (based on ITT population), either by performing a regression or by finding utility decrements in the literature.
d. Adapt the model by
   - removing the on treatment utility increment,
   - incorporating utility decrements for each separate AE,
   - incorporating per-event costs for AEs for the pre- and post-docetaxel treatment phases as well.

B4. **Priority Question**: **Estimation of prediction equations (Appendix 16 MS) -** ***Issues that may introduce bias and need additional analyses and an updated model***

a. Figure 37 shows that the time to discontinuation is similar in the selected group used in the model (analysable data set of 902 patients with information on baseline characteristics) and the ITT group for best supportive care but that time to discontinuation appears higher for abiraterone in the modelled group compared with the ITT population. The manufacturer concluded that times to APP/BSC (PP) discontinuation for the 902 people with analysable data are similar to the ITT group.
   - Please provide the results of analyses to determine the similarity of TTD and OS in the ITT group and the selected group of 902 people used in the model.
   - Please provide an updated version of all prediction equations incorporating all ITT patients (with censoring at the time patients deviated from the pathway specified in the model; thus including patients with missing baseline data), with assigned treatment (i.e. BSC (PP), AAP) included as only covariate if significant at p-value of 0.10 (thus excluding other baseline characteristics as this information is missing in a subset of the patients). For this purpose,

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please perform the model selection (exponential, Weibull, log-normal or log-logistic distribution) as performed for the prediction models described in Appendix 16 and provide the AIC and BIC statistics.
    - Please provide graphs comparing the observed KM-curve for these updated prediction equations (from the ITT population with censoring at the time patients deviated from the pathway specified in the model). Please add the number of patients at risk to the graphs (reported per 0.5 year).
    - Please provide updated cost-effectiveness results and an updated version of the DES model with these updated prediction equations. For this purpose, the proportion of patients for whom docetaxel treatment is unsuitable might be calculated from observed data from the COU-AA-302 trial (instead of based on ECOG PS <2).
b. For the selection of covariates in the prediction equations, it is stated (Appendix 16): *"A p value of 0.10 was used to decide which variables had a univariate association. Significant predictors were then combined in a multivariate model, which was then manually trimmed to exclude predictors that become non-significant (p>0.1)."* However some covariates with a higher p-value than 0.10 were included in the model.
    - Please provide the prediction equations and updated cost-effectiveness results when excluding the covariates and interaction terms with a larger p-value than the apprehended threshold of 0.10.
    - Please provide an updated version of the DES model with these updated prediction equations.
    - Please provide graphs comparing these prediction equations and the observed KM-curves (from the ITT population with censoring at the time patients deviated from the pathway specified in the model). Please add the number of patients at risk to the graphs (reported per 0.5 year).
c. The DES model does not include the possibility of dying during AAP and BSC (PP). As some patients (N=5) died before AAP or BSC (PP) treatment end, it is appropriate to included probabilities to die during all phases in the model. The same applies for death during post-docetaxel treatment:
    - Please provide an updated DES model that incorporates the possibility of dying during AAP or BSC (PP) treatment and during post-docetaxel treatment and updated cost effectiveness results.,
    - Please provide graphs comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) to these updated prediction equations. Please add the number of patients at risk to the graphs (reported per 0.5 year).

B5. **Priority Question**: **Estimation of prediction equations (Appendix 16 MS) -** ***Issues that are unclear or needed to examine the validity of the current model***

a. In appendix 16 (P298-299) it is stated: *"Observed Kaplan–Meier curves and cumulative hazard functions were examined graphically. If the exploratory analysis indicated that the shape of the cumulative hazard was similar in both treatment arms,*

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then the two arms were modelled together and a treatment indicator was included as a predictor in the model; otherwise, each treatment arm was modelled separately."

- Please provide the observed Kaplan–Meier (KM) curves and cumulative hazard functions for all equations that were used to perform the graphical examination.
- Time from AAP/BSC (PP) end to death, unlike all other prediction equations, was estimated separately by arm (see Table 148). Please provide an updated version of the 'Time from AAP/BSC (PP) end to death' prediction equations using a single prediction equation for both arms (AAP and BSC (PP)) and a coefficient for treatment arm.

b. It is unclear which candidate predictors are used for which prediction equation. Please list for each prediction equation separately, all candidate predictors and mark those that were significant in the initial univariate selection and also mark those that were significant in the multivariate model. In addition provide for each candidate predictor the p-value in the univariate selection and if applicable the p-value in the multivariate model.

c. Considering model selection for the prediction equations:
   - How were the models selected in case the AIC and BIC were inconsistent on the best-fitting model?
   - Please clarify whether the AIC and BIC statistics reported in Table 142 were based on the prediction equations with selected covariates included? If not, please provide these statistics.
   - Please also clarify how the validity of the extrapolation was assessed, as fit to the observed data is not necessarily a good indication.

d. In appendix 16 it is stated: *"Commonly used distributions such as exponential, Weibull, log-normal, and log-logistic were tested, and the one yielding the closest fit to the observed data was chosen (refer to the Model selection section below for details). Best fitting does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data. To ensure this was not the case, the observed versus predicted distributions by treatment group were examined."*
   - Please provide graphs comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) and the predictions using the four distributions (not only the best-fitted distribution) that were examined for selecting the distribution (Exponential, Weibull, log-normal or log-logistic). Please add the number of patients at risk to the graphs (reported per 0.5 year).
   - Please provide the coefficients and standard errors for all these prediction equations.

B6. **Priority Question**: **Comparison of model outcomes and trial outcomes**

Table 68 provides a useful summary of the proportion of patients in the pre-docetaxel, on-docetaxel and post-docetaxel phases of the model, and the respective duration of time spent in that treatment phase. However, it is not possible to compare this to the observations in the subset of the trial population that followed pathways relevant to the UK setting.

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a. Please provide these data for people receiving treatments after AAP/BSC corresponding to scenarios included in the model [figures 39 and 40] as observed in the COU-AA-302 trial (ITT population with censoring at the time patients deviated from the pathway specified in the model,) using exactly the same format as Table 68.

B7 Currently, it is not possible to validate predicted data versus observed data for each (treatment) phase in the DES model. Please provide: the graphs for all prediction equations currently used in the DES model comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) to the prediction equations used in the model (Appendix 16). Please add the number of patients at risk to the graphs (reported per 0.5 year).

B8. It is unclear why patients in the BSC arm were censored after sequential AAP and Cabazitaxel treatment (post-docetaxel). The addition of Cabazitaxel could be corrected for (as done for the other pathways).

a. Please provide updated prediction equations, wherein patients in the BSC arm are not censored after sequential AAP and Cabazitaxel treatment.
b. Please provide graphs comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) to these updated prediction equations.
c. Please add the number of patients at risk to the graphs (reported per 0.5 year).
d. Please also provide an updated version of the 'negative treatment effect' for cabazitaxel using the same format as Table 35.

B9. Figure 11 is useful to understand the model structure, but unclear in distinguishing between types of BSC (e.g. active treatment and palliative treatment).

a. Please provide an updated figure with a distinction between different types of BSC

Section C: Clarification on literature searches

Search strategies: General questions

C1. Please clarify whether the flow-diagrams report results from the update searches described in the submission. Are the results from the original searches conducted for NICE TA259 also included in the flow-diagrams?

Search strategies: Clinical effectiveness and adverse events (Sections 6.1, 6.8, 6.9, Appendices 10.2, 10.6 and 10.8)

C2. Please clarify whether validated study design search filters were used for the RCT and non-RCT facets. If validated filters were used, please provide details of the source or reference of those filters.

C3. There appears to be an error in the date span used for the third Embase/Medline update search strategy (Table 100). The search was conducted on 27.09.12, and the

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date limit used in the strategy was '[27-09-12]/sd'. Please confirm whether the search was limited to one day or whether this is a reporting error. If the search was limited to a single day, please clarify the implications of potentially excluding references for the full date span.

C4. Please provide more details for the searches of conference proceedings, i.e. search strategies or search terms used, website addresses

Search strategies: Cost effectiveness (section 7.1, appendix 10.10)

C5. Please explain why the cost-effectiveness searches used a date span that started from 2000.

C6. Despite reporting that the searches run from 2000, the first update search strategy for Embase/Medline appears to run from 14-12-2009 to 9-6-2011 (Table 116, search line #92). Please confirm whether the search was limited to this date span or whether this is a reporting error. If the search was limited to this date span, please clarify the implications of potentially excluding references for the full date span.

C7. The second update search strategy reports a date span of 20-11-2012 to 30-5-2013 (Table 117, search line #92). This would mean that over a year has been missed since the previous update search. Please clarify whether this is a reporting error, or whether the search conducted using this date span. Please clarify the implications of potentially missing references for this date span.

C8. In section 7.1.1 it is stated that conference proceedings from ISPOR International and ISPOR European conferences were hand searched. There are no details of these searches in 10.10. Please provide details for these searches.

C9. Please explain why there are no Emtree (or MeSH) subject index terms for the named interventions in the Embase/Medline and Cochrane Library search strategies (Tables 116-121). Please clarify what impact this may have had on the search results.

Search strategies: Health related quality of life (section 7.4, appendix 10.12)

C10. In section 7.4.5 and 10.12.3 it is stated that the date span of the searches was from 2005 to 2013. However, the search strategies for embase.com and the Cochrane Library (Tables 130-131) indicate that the date span used was 2005 to 2012. Please confirm whether this is a reporting error or if the searches were conducted using this date span.

C11. There appears to be a mistake in the final search line of the Cochrane Library (NHS EED) search strategy (Table 131, search line #8). Please confirm whether this is a reporting error or if the search lines #1 and #2 were combined for this search.

C12. Please clarify whether an update search in EconLit was conducted. It is not clear from section 10.12.1 whether this search was conducted or not.

Executive summary

C13. Please clarify the anticipated submission date to the Scottish Medicines Consortium for its appraisal of abiraterone.

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