janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Janssen's Response to the Appraisal Consultation Document

Prostate cancer (hormone relapsed, metastatic) - enzalutamide (after docetaxel)

Please find below Janssen's response to the revised Appraisal Consultation Document (ACD) for enzalutamide issued in January 2014. We are pleased to have an opportunity to provide our comments in relation to the interpretation of the cost-effectiveness evidence and reiterate our support for NICE to make additional treatment options available to patients with mCRPC.

1. The rapid approval of several novel agents in recent years has given prostate cancer patients and their treating physician new and effective therapeutic options. With the rapid introduction of these agents to routine clinical practice, questions will inevitably arise about their optimal sequencing in the context of existing therapies, with further evidence needed to fully define how best to use these agents, in which patients and in which sequence.

   Overall, there are no robust data currently available that could determine the appropriate sequencing of the newer agents approved to treat mCRPC, particularly since the clinical trials investigating these agents were completed in a very quick timeframe and the development programs overlapped one another. In the absence of this, the choice of which NICE-approved agent to use in a patient should be determined by individual clinicians based on clinical need and efficacy.

   According to the draft decision by the National Institute for Health and Care Excellence (NICE) released on 28th January 2014, NICE is consulting on a proposal to recommend enzalutamide in men with metastatic castration-resistant prostate cancer who have been treated with docetaxel, but who have not yet received prior treatment with abiraterone.

   i. This decision puts clinicians and patients in a difficult situation as they are being faced with a very difficult dilemma. As well as having to select which treatment will work better for a particular patient, they do so knowing that if they opt to prescribe abiraterone, they are ruling out the possibility of prescribing enzalutamide later on. Likewise, the guidance could inadvertently be misinterpreted to mean that abiraterone is allowable after enzalutamide, but not vice versa. This would cause sequencing by default, which is exactly what the ACD was seeking to avoid.

   ii. Our concern is that incorporating such a statement into the guidance would be prejudicial against Janssen. The guidance as currently worded creates a natural inequity against abiraterone acetate simply because of the timing of the appraisals and risks Janssen being disadvantaged purely for being first to

market. This is because there is no mention of enzalutamide in NICE's abiraterone guidance (as one would expect as enzalutamide was not licensed at the time of issue), but abiraterone is referenced in the enzalutamide guidance. The unintended consequence of this may be to infer that physicians should use enzalutamide first followed by abiraterone. We have already seen evidence of this interpretation in some units following enzalutamide's similar approval on the National Cancer Drugs Fund.

iii. Thirdly, this is a move that limits patient access through the introduction of unnecessarily restrictive wording that compounds a situation in which treatment options are already limited at this stage of the patient pathway.

2. In our initial response to consultation, we highlighted two key points in relation to the following:

   i. The indirect comparison presented by the manufacturer does not utilise the most comparable datasets (Section 3.11, 3.12 and 3.18 of the ACD)

   ii. Assumptions made by the manufacturer about the HR for OS and treatment duration in the economic analysis are subject to significant uncertainty (Sections 4.9 and 4.10 of the ACD)

We note that whilst the committee acknowledged the concerns that were raised in relation to time-dependency and potential bias against abiraterone, the proposed solution of using more mature datasets does not explicitly address the shortcomings in the manufacturer analyses (Janssen response to consultation November 2013). In this regard, particularly around the comparability of the datasets used and differences between the trials, we would like to reiterate our initial concerns documented in our original response to the first enzalutamide ACD in November 2013.

We note that a number of clinical experts (in the manufacturer's own words) believe that enzalutamide and abiraterone have the same clinical effect (page 25). Given that the manufacturer's indirect comparison showed no statistically significant difference for overall survival (page 36), the potential inference from the ACD that enzalutamide is superior to abiraterone is a gross misinterpretation of the evidence presented by Astellas and somewhat misleading, if not wholly inaccurate.

We propose that necessary caveats are introduced explicitly in the revised ACD to highlight the fact that, whilst the point estimates in the indirect comparison presented to the committee suggest a difference in treatment effect between enzalutamide and abiraterone, this difference is not substantiated either clinically or statistically.