Cost effectiveness of abiraterone acetate (Zytiga®) for the treatment of metastatic castration resistant prostate cancer patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

The NCPE has issued a recommendation regarding the use of abiraterone acetate for this indication. The NCPE do not recommend reimbursement of abiraterone acetate.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (Janssen) economic dossier on the cost effectiveness of abiraterone acetate. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. As this is an oncology drug, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2014**

Cost effectiveness of abiraterone acetate in the treatment of metastatic castration resistant prostate cancer (mCRPC) patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Janssen submitted an economic evaluation on the cost effectiveness of abiraterone acetate for this indication, to the National Centre for Pharmacoeconomics (NCPE) in September 2013. The NCPE requested clarification on a number of issues; the final Economic Model and Budget Impact Model were submitted in February 2014.

The economic evaluation investigated the cost effectiveness of abiraterone acetate (+ prednisolone) versus prednisolone (+ placebo). The evaluation was from the Health Service Executive perspective, through the High Tech Drugs Scheme.

According to the model, which adopts a patient level simulation with a lifetime horizon, a patient begins treatment with abiraterone acetate (+ prednisolone) or prednisolone (+ placebo). He/she may discontinue treatment due to disease progression or an AE. Patients who discontinue either move to docetaxel after a treatment free interval or die having only received best supportive care. A patient who starts docetaxel will be at risk of treatment discontinuation or death. Patients who survive docetaxel may receive a post-docetaxel treatment (abiraterone acetate for the prednisolone (+ placebo) arm, or best supportive care for the abiraterone acetate (+ prednisolone) arm) after a treatment free interval, or die having only received best supportive care. Patients who receive post-docetaxel active treatment are at risk of treatment discontinuation. Once post-docetaxel treatment is discontinued, patients remain on best supportive care until death.

Patient-level data from the COU-AA-302 pivotal study [1] was used to inform time spent in the each period of the model treatment pathway.

COU-AA-302 is a multinational, multicentre, double-blind placebo-controlled study, in which 1,088 patients (April 2009-June 2010) with asymptomatic/mildly symptomatic mCRPC post-androgen deprivation therapy were randomly assigned to

receive abiraterone acetate (1000 mg once daily) plus prednisone (5 mg BD) or placebo plus prednisone [1].

Co-primary end points were radiographic progression-free survival (PFS) and overall survival (OS). The economic model inputs are based on the third planned interim analysis (May 2012; 55% of deaths; median follow-up = 27.1 months). At this interim analysis, OS was 35.3 months (abiraterone acetate + prednisolone) vs. 30.13 months (prednisolone + placebo), HR= 0.79; 95% CI: 0.66-0.96; p=0.015, the O'Brien-Fleming efficacy boundary was not crossed; a statistically significant OS advantage for abiraterone acetate (+ prednisolone) was not detected. Grade 3/4 adverse events were reported in 49.3% vs. 43.5% of abiraterone acetate (+ prednisolone) and prednisolone (+ placebo) patients respectively (safety population). Adverse events of special interest (including hypertension, hypokalaemia and fluid retention, cardiac disorders, and hepatotoxicity) were reported in 66% and 50% of the abiraterone acetate (+ prednisolone) and prednisolone (+ placebo) groups respectively.

The basecase assumes that patients were not eligible for cabazitaxel after docetaxel. Therefore, they will not receive active treatment after docetaxel, even though they might have received cabazitaxel in COU-AA-302. It is also assumed that these patients will not receive retreatment with abiraterone acetate. As cabazitaxel prolongs both PFS and OS compared to best supportive care/prednisolone post-docetaxel, the efficacy results had to be adjusted with respect to the clinical benefits associated with cabazitaxel in COU-AA-302. Therefore the active treatment-eligible group in the abiraterone acetate arm who do not take post-docetaxel active treatment in the model follow the same survival observed in COU-AA-302 trial with a negative treatment effect based on the COU-AA-301 data [2]. (COU-AA-301 compared abiraterone acetate (+ prednisone) and prednisone (+ placebo) in patients with mCRPC who had previously received docetaxel).

On the whole, the costs which were input into the model were valued credibly. Irish costs were used where available. A number of the costs, applied to the Grade 3/4 adverse events, were obtained from UK NHS Cost Data. The use of non-Irish data will have introduced uncertainty into the economic evaluation.

The Health Related Quality of Life (HRQoL) of patients in COU-AA-302 and COU-AA-301 were measured using the Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire. The FACT-P scores were mapped to EQ-5D scores; the EQ-5D scores were input into the model. While the Review Group consider this approach to be appropriate it is not immediately clear how many patients were involved in HRQoL elicitation; this may be a source of uncertainty.

The assessment was submitted in September 2013; as such cost and consequences were discounted at 4% per annum.

In the original company Submission, the basecase ICERs (abiraterone acetate (+ prednisolone) vs. prednisolone (+ placebo)) were €133,594/LYG (incremental cost= €80,620; incremental LYG=0.60) and €156,513/QALY (incremental QALY=0.52). This analysis assumed that patients will not receive active treatment after docetaxel. It also included a cost of granulocyte colony-stimulating factor (G-CSF) for the treatment of febrile neutropenia.

A revised basecase, requested by the NCPE to include the post-docetaxel treatment with cabazitaxel (in both arms) and the prophylactic use of G-CSF in 30% of patients (with no G-CSF to treat established febrile neutropenia) was presented. The resultant ICERs were €151,518/LYG (incremental cost = €85,466; incremental LYG=0.56) and €171,384/QALY (incremental QALY=0.50). The Review Group believe that these ICERs are more likely to reflect the cost effectiveness of abiraterone acetate for this indication. However, for this analysis, in the absence of an indirect comparison or a meta-analysis, the PFS and OS outcomes for cabazitaxel and abiraterone acetate, in the post-docetaxel treatment phase, were assumed to be the same. This approach will introduce some uncertainty into the evaluation.

We note that this economic evaluation assumes a first line AAP compliance rate of 98%; real world compliance is likely to be lower.

The model results are sensitive to changing a number of parameters, notably the utility values (which are uncertain), parameter extrapolation of treatment duration

data (which is uncertain) and the model time horizon. The ICER increases when a 5% discount rate (for costs and consequences) is applied.

The probabilistic analysis was performed on the original Submission model (basecase ICER = €156,513/QALY), it is therefore likely to be conservative. It indicates that there is a 0% probability that abiraterone acetate (+ prednisolone) is cost effective at a payer threshold ≤ €105,000/QALY.

The NCPE Review Group conclude that, at the current price, abiraterone acetate (+ prednisolone) is not a cost effective treatment for mCRPC patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

1. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy (for the COU-AA-302 Investigators). New England Journal of Medicine 2013;368(2):138-148.
2. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer (for the COU-AA-301 Investigators). New England Journal of Medicine 2011;364(21):1995-2005.