Economic evaluation of Abiraterone Acetate (Zytiga®) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior docetaxel-based chemotherapy.

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Abiraterone acetate is licensed with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after docetaxel based chemotherapy. Abiraterone acetate a pro-drug of abiraterone, is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 (CYP c17) thereby blocking androgen synthesis by the adrenal glands and testes and within the prostate tumour. A full pharmacoeconomic assessment was submitted by the manufacturer Janssen on the 12th December 2011.

The economic submission evaluated the cost effectiveness of abiraterone acetate 1,000mg once daily in combination with prednisolone 10mg/day for the treatment of patients with metastatic castration resistant prostate cancer who have received prior docetaxel based chemotherapy. There were 2 comparator therapies included in the evaluation. The first comparator was prednisolone 10mg once daily. The alternative comparator was a combination of mitoxantrone (12mg/m^2 every 3 weeks) plus prednisolone 10mg/day. Prednisolone monotherapy was used as a proxy for best supportive care in this analysis. The evaluation was conducted from the Irish Health Service Executive (HSE) perspective.

The efficacy and safety data for abiraterone acetate was based on the phase III clinical trial by the COU-AA-301 investigators (N. Engl. J. Med 2011;364:1995-2005). In this phase III clinical trial 1195 patients who had previously received docetaxel were randomly assigned in a 2:1 ratio to receive 5mg of prednisolone twice daily with either 1000mg of abiraterone acetate (797 patients) or placebo (398 patients). The primary endpoint for the trial was overall survival. Secondary endpoints included time to prostate-specific antigen (PSA) progression, progression-free survival according to radiologic findings based on prespecified criteria and the PSA response rate.

After a median follow-up of 12.8 months overall survival was 14.8 months in the abiraterone acetate-prednisolone group as compared with 10.9 months in the placebo-prednisolone group (hazard ratio 0.65;95% confidence interval, 0.54-0.77:P<0.001). All secondary endpoints, including time to PSA progression (10.2 vs 6.6 months;P<0.001), progression free survival (5.6 months vs 3.6 months;P<0.001) and PSA response rate (29% vs 6%;P<0.001) favoured the treatment group. The median duration of treatment was 8 months in the group that received abiraterone acetate plus prednisolone and 4 months in the group that received placebo plus prednisolone

A survival based decision analysis model with three health states was programmed in Microsoft Excel. Patients entered the model in a progression free health state in which they received active treatment. Patients who experienced disease progression and did not die transitioned to the progressive disease health state where they no longer received active anti-cancer treatment. At the end of each model cycle (3 weeks) a patient could remain in any health state or progress, but could not regress. Patients could enter the death health state at any time. The number of patients remaining in each health state at each model cycle was calculated by the overall survival and progression free survival curves, which were derived from patient-level clinical trial data or published literature for each comparator.

In the economic evaluation 3 different types of costs associated with the interventions were included. These were the costs of drug administration, cost of patient monitoring and drug costs. The cost of adverse events was also considered particularly grade 3 or 4 adverse reactions which were a significant differentiating factor among the model comparators. The economic model also considered the impact of long-term medication costs after the occurrence of certain adverse events. Unplanned, event related medical resource utilisation costs, terminal costs and subsequent therapy costs were also included in the model.

Within the COU-AA-301 Trial health related quality of life was measured using the prostate cancer specific Functional Assessment of Cancer Therapy – Prostate (FACT-P) instrument. In order to transform FACT-P values into preference adjusted health status values the FACT-P scores where mapped to EQ-5D scores. Based on

mapping FACT-P to EQ-5D the estimated baseline utility of mCRPC patients was 0.773. An incremental treatment effect of 0.045 was applied to all patients receiving abiraterone acetate and mitoxantrone in the progression free health state. A disutility per grade III/IV adverse event of -0.078 was applied to the incremental rate of each adverse event of chemotherapy vs abiraterone acetate. Following disease progression a utility value of 0.5 was applied. Costs and consequences were discounted at 4% per annum.

The primary outcomes reported in the model were incremental cost per quality adjusted life year (cost/QALY) and incremental cost per life year gained (cost/LYG). In the basecase analysis the incremental cost-effectiveness ratio (ICER) for abiraterone acetate plus prednisolone vs prednisolone monotherapy was €135,454/QALY or €142,367/LYG. The ICER for abiraterone acetate plus prednisolone vs mitoxantrone plus prednisolone was €160,388/QALY or €130,708/LYG. A subgroup analysis of patients who received one prior chemotherapy regimen was also included. In this subgroup the ICER for abiraterone acetate plus prednisolone vs prednisolone monotherapy was €118,031/QALY or €116,110/LYG. For abiraterone acetate plus prednisolone vs mitoxantrone plus prednisolone the ICER was €144,485/QALY or €108,737/LYG in this cohort. All ICER values exceed the cost-effectiveness threshold levels considered by the HSE i.e. € 45,000/QALY and € 20,000/QALY.

For the univariate sensitivity analysis the time horizon had the largest impact on the ICER e.g. a four year time horizon increased the ICER vs prednisolone monotherapy from €135,454/QALY to €144,211/QALY and vs mitoxatrone plus prednisolone the ICER increased to €174,482/QALY. As expected, varying the discount rate for costs and benefits influenced the ICER. Changing the extrapolation methodology beyond the trial period for overall survival from constant hazard rate to Weibull parametric functions increased the ICER to €137,907/QALY vs prednisolone and €164,288/QALY vs mitoxantrone plus prednisolone. In relation to utility inputs the basecase utility for mCRPC had the greatest influence on the ICER. In relation to costs, model inputs had a relatively small impact on the model results. The probabilistic sensitivity analysis indicated that abiraterone plus prednisolone had a 0% probability of being cost-effective for all ICER's up to €132,000/QALY.

The company submitted budget impact estimates in the economic dossier. The eligible patient population was estimated from data provided by the National Cancer Registry of Ireland (NCRI) and experience of Janssen Ltd with the abiraterone acetate patient access scheme in Ireland. The number of eligible patients was estimated at 150 in 2011 increasing to 162 by 2015. The annual treatment cost for abiraterone acetate plus prednisolone was estimated at €28,546 assuming an abiraterone acetate price of €3,488.06 per month. Year 1 costs were estimated at €858,747 increasing to €2.7million in 2015. The NCPE calculations indicate that treatment with abiraterone acetate plus prednisolone would result in a cumulative budget impact of €9.84million over the first 5 years.

The NCPE review group believe that, at the submitted price, abiraterone acetate (Zytiga®) is not cost-effective for the treatment of patients with mCRPC in patients who have received prior docetaxel based chemotherapy. The ICER values are well above the threshold levels of interest to the HSE i.e. € 45,000/QALY and € 20,000/QALY. The results of this economic evaluation will be considered by the National Cancer Control Programme (NCCP).