Cost Effectiveness of enzalutamide (Xtandi®) for the treatment of adults with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the use of enzalutamide for this indication. The NCPE do not recommend reimbursement of enzalutamide.

The HSE has asked the NCPE to evaluate the manufacturer's (Astellas Pharma Co Ltd) economic dossier on the cost effectiveness of enzalutamide. 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 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 **April 2014**

Cost Effectiveness of enzalutamide (Xtandi®) for the treatment of adults with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel.

1. In October 2013, Astellas Pharma Co Ltd submitted an economic evaluation to the National Centre for Pharmacoeconomics (NCPE) on the cost effectiveness of enzalutamide for the treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy. Updates to the dossier were submitted in December 2013. Further clarifications on a number of issues were sought by the NCPE in March 2014.

   Three comparators were considered: best supportive care (BSC), abiraterone acetate (with prednisolone + BSC) (referred to as abiraterone hereafter) and cabazitaxel (with prednisolone + BSC) (referred to as cabazitaxel hereafter). The evaluation was from the Health Service Executive (HSE) perspective, through the High Tech Drugs Scheme.

   The evaluation uses a Markov model with a 10 year time horizon. Patients with mCRPC who have progressed on or after docetaxel enter the model in the Stable Disease state. When patients die they move to the Dead state, while those who progress move to the Progressive Disease state. Patients may remain in the Progressive Disease or move to the Dead state.

2. No head-to-head study comparing enzalutamide with abiraterone or cabazitaxel have been conducted. For this submission, efficacy and safety data comparing the effect of the three drugs on key endpoints of interest was derived from an indirect treatment comparison of pivotal RCTs using the Bucher *et al* methodology [1]. The studies included in the comparison are COU-AA-301 (abiraterone (+ prednisolone) vs. prednisolone) [2], TROPIC (cabazitaxel (+ prednisone) vs. mitoxantrone (+ prednisone)) [3] and AFFIRM [4].

3. AFFIRM was a multinational, phase III, randomised, double-blind, placebo-controlled study in which 1199 men with mCRPC (previously treated with docetaxel-based chemotherapy) were randomly assigned (2:1) to enzalutamide or

placebo [4]. Patients in both arms received BSC in addition to the study treatment. The placebo arm is referred to as BSC in this submission. The primary endpoint was overall survival (OS), defined as the time from randomisation to death from any cause in the intention-to-treat population.

The study was stopped after a pre-specified interim analysis (Sept 25th 2011) (median follow-up of 14.4 months) at 520 deaths. Median time on treatment was 8.3 months (enzalutamide) vs. 3.0 months (placebo). Enzalutamide was associated with a significantly longer median OS (18.4 months: 95% CI: 17.3, not reached) than placebo (13.6 months; 95% CI: 11.3, 15.8); p<0.0001. Enzalutamide significantly reduced the risk of mortality vs. placebo; hazard ratio (HR) for death = 0.631; 95% CI: 0.539, 0.752 (p<0.0001). Secondary outcomes in the enzalutamide and placebo groups were measured; the health related quality of life (HRQoL) response rate (according to FACT-P) was 43% vs. 18% (p<0.001), time to PSA progression was 8.3 vs. 3.0 months, HR=0.25 (p<0.001), investigator assessed radiographic progression-free survival (rPFS) was 8.3 vs. 2.9 months, HR=0.40 (p<0.001), and time to the first skeletal-related event was16.7 vs. 13.3 months, HR= 0.69 (p<0.001). Independently assessed rPFS was not measured. Adverse events (AEs) (≥ Grade 3) occurred in 45.3%, and 53.1% of the enzalutamide and placebo groups respectively. Cardiac disorders were recorded in 6% and 8% of the enzalutamide and placebo arms (Grade 3 in 1% and 2%, respectively). Seizures were reported in 0.6% of the enzalutamide arm.

Utility scores were derived from a mapping study which estimated EQ-5D utilities from the disease specific FACT-P. EQ-5D and FACT-P data were both collected in AFFIRM. FACT-P data was collected from all AFFIRM patients, whilst the EQ-5D was administered only in France, Germany, Italy, Spain, and the UK. The evaluable FACT-P responses amounted to 81% and 64% for the enzalutamide and placebo arms respectively, whilst there were EQ-5D evaluable responses for 18% and 17% for the respective arms. The small number of evaluable EQ-5D responses will have introduced uncertainly into these values.

An independent data and safety monitoring committee recommended the study be halted and unblinded after this pre-specified interim analysis. Eligible patients in

the placebo arm were offered enzalutamide. At database lock (December 2011) 344 deaths had occurred in the enzalutamide arm and 232 in the placebo arm. Median follow-up was 15 months; enzalutamide was associated with a significantly longer median OS (17.8 months, 95% CI: 16.7, 18.8) than placebo (13.3 months, 95% CI: 11.2, 14.2). Enzalutamide significantly reduced the risk of mortality by 38.2% compared to placebo (stratified HR = 0.618, 95%CI: 0.523, 0.730; p<0.001). It is this data which is used in the economic evaluation. The NCPE Review Group note that OS data up to database lock was used for the model, however the efficacy inputs for the cost-effectiveness model are not adjusted for trial cross-over. This will have introduced uncertainty into the economic evaluation, although the impact is likely to be conservative for enzalutamide.

4. For the indirect comparison, the control arms of AFFIRM, COU-AA-301 and TROPIC are considered to be the common arm. The COU-AA-301 double-blind, placebo-controlled trial compared abiraterone (+ prednisolone) to prednisolone in post docetaxel mCRPC patients [2]. The TROPIC open-label randomised trial compared cabazitaxel (+ prednisone) to mitoxantrone (+ prednisone) in post docetaxel mCRPC patients [3]. The indirect comparison assumes that these control arms are comparable. This assumption is uncertain. The definitions of OS, PSA response and objective response rate were the same in the three trials. Time to first skeletal-related event and rPFS were not assessed in TROPIC. To compare PFS in all studies, a modified PFS (mPFS) was derived post-hoc. This was defined as the composite endpoint of time to radiographic progression, first skeletal-related event or death due to any cause, whichever occurred first.

   The indirect treatment comparison also assessed tolerability and incidence of AEs (all Grades) and AEs (Grade ≥ 3). However, only the comparison between enzalutamide and abiraterone was possible. It was not possible to compare enzalutamide and cabazitaxel due to the differences in the nature of the AEs between enzalutamide and cabazitaxel and between placebo and mitoxantrone. This will introduce uncertainty into the economic evaluation of enzalutamide vs. cabazitaxel.

The indirect comparison indicates that when compared with abiraterone, enzalutamide was associated with a non significant increase in OS, a significantly higher likelihood of attaining rPFS, mPFS and PSA response, and a significantly longer time to treatment discontinuation. No significant difference was observed for time to first skeletal-related event or likelihood of attaining objective response rate.

When compared with cabazitaxel, enzalutamide was associated with a significantly higher likelihood of attaining mPFS, ORR and PSA response. No significant difference was observed for OS.

This indirect comparison is unpublished and has not been peer reviewed. The comparison is limited by the different median follow-ups in the various trials, the difference in designs of the trials, the slight differences in the baseline patient characteristics, the assumption that the different control arms are equivalent and the lack of consistency of the PFS data (and the subsequent mPFS data derived post-hoc). Also, an indirect comparison of AEs between enzalutamide and cabazitaxel was not possible. Thus, the comparisons of enzalutamide with abiraterone and cabazitaxel are associated with more uncertainty than the comparison with BSC.

5. For the economic model, the BSC empirical data from AFFIRM was chosen as the reference arm for the survival analyses. This empirical data was extrapolated using parametric survival models. The Log-Logistic Model was the best statistical fit (AIC/BIC) for both the overall survival (OS) reference curve and the progression free survival (PFS) reference curve. This model was used in the basecase evaluation. In addition, the Weibull Model was used in a scenario analysis. The enzalutamide, abiraterone and cabazitaxel strategies were then modelled by applying hazard ratios to the reference curves.

6. For the economic evaluation, on the whole all the important and relevant costs and consequences were identified and valued credibly. The evaluation assumes that the HSE pays the full list prices for abiraterone and cabazitaxel; these costs may

not be reflective of the current cost of these comparators to the HSE.

7. As was recommended at the time of submission, a 4% discount rate on costs and consequences was assumed; the ICERs were €60,738/QALY (vs. abiraterone), €75,311/QALY (vs. cabazitaxel) and €98,949/QALY (vs. BSC). Changing the discount rate to 5% [5] has only a small impact on these ICERs. The probabilistic analysis (PSA) indicates that the probabilities of enzalutamide being cost effective are 7% (vs. abiraterone), 0% (vs. BSC) and 4% (vs. cabazitaxel) at a payer threshold of €45,000/QALY. The ICERs and PSA results are sensitive to the discount applied to the comparators; their costs in the model may not be reflective of their current cost to the HSE.

   The economic evaluation assumes a 100% compliance rate; this is in accordance with the median compliance rate observed in AFFIRM. This is unlikely to reflect real world experience. Further, the compliance rate in COU-AA-301 was 98% [2] and the median relative dose intensity in the cabazitaxel arm of TROPIC was 96.1% [3].

8. The economic evaluation results are sensitive to changing a number of model inputs, notably the efficacy data from AFFIRM (which is uncertain), the parameter extrapolation of PFS and OS data (which is uncertain), utility gains associated with enzalutamide and abiraterone (which are uncertain), the model time horizon and the assumed cost of the comparators in the model.

9. The NCPE Review Group concludes that, at the current price, enzalutamide is not cost effective for the treatment of adults with mCRPC whose disease has progressed on or after docetaxel. This analysis assumes that the HSE pays the full list prices for abiraterone and cabazitaxel.

References

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