



**Cost Effectiveness of enzalutamide (Xtandi<sup>®</sup>) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.**

The NCPE has issued a recommendation regarding the use of enzalutamide for this indication. The NCPE does not recommend reimbursement of enzalutamide at the submitted price.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the Applicant's (Astellas Pharma Co Ltd) economic dossier on the cost effectiveness of enzalutamide (Xtandi<sup>®</sup>). 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 that 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 that may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, 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.

## **Background**

Astellas Pharma Co Ltd submitted a dossier to examine the cost effectiveness of enzalutamide (Xtandi<sup>®</sup>) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

### **1. Comparative Effectiveness**

Comparative data for enzalutamide versus best supportive care was taken directly from the double-blind, phase III PREVAIL study<sup>[1]</sup>. In the study 1,717 patients were randomly assigned to receive either enzalutamide (at a dose of 160 mg) or placebo (best supportive care) once daily. The co-primary end points were radiographic progression-free survival (central (independent) review) and overall survival.

At the pre-specified data cut-off date for the primary radiographic progression-free survival analysis, treatment with enzalutamide had resulted in a significant reduction in risk of radiographic progression (central review) or death versus placebo; hazard ratio (HR) 0.186 (95% CI 0.149 - 0.231). At a subsequent data cut-off, a significantly lower risk was also observed for investigator-assessed radiographic progression (HR 0.307; 95% CI 0.267 - 0.353). At the planned interim analysis of overall survival, enzalutamide was associated with a significantly longer median overall survival (32.4 months; 95% CI 30.1 - not yet reached) than placebo (30.2 months; 95% CI 28.0 - not yet reached). Fewer deaths had occurred in the enzalutamide group; HR 0.71; 95% CI, 0.60 to 0.84;  $p < 0.001$ .

Overall survival data for the cost-effectiveness model was analysed from an additional data cut. The study had been unblinded prior to this cut-off and therefore the data will be prone to bias. No survival status validation was performed at this cut-off and therefore the data will be prone to uncertainty. A significantly lower risk of death was observed with enzalutamide. After adjustment for cross-over (inverse probability of censoring weighted methodology), enzalutamide was still associated with a significant reduction in the risk of death. This adjustment corrected for the proportion of patients in both arms of PREVAIL who received 2<sup>nd</sup> line post-study drug treatments that are not considered to be part of the standard treatment pathway in Ireland (including abiraterone, enzalutamide, cabazitaxel and sipuleucul-T).

No head-to-head comparison of enzalutamide and abiraterone has been conducted. The Applicant has therefore presented an indirect treatment comparison mediated via the control arms of the PREVAIL trial and the phase III, double-blind COU-AA-302 trial (abiraterone (+ prednisone) vs. placebo (+ prednisone)). For the indirect treatment comparison, both comparator arms were assumed to be similar which may not be the case. The different exposure to corticosteroids in the two control arms is the main limitation to the indirect treatment comparison. The indirect treatment comparison is unpublished and has not been peer-reviewed. According to this indirect treatment comparison, when compared with abiraterone, enzalutamide is associated with a significantly lower likelihood of investigator-assessed radiographic disease progression, PSA progression, initiation of cytotoxic chemotherapy and Health Related Quality of Life (HRQoL) deterioration. No significant differences were observed between enzalutamide and abiraterone for either adjusted (for cross-over) or unadjusted overall survival.

## **2. Safety**

In the PREVAIL safety population, adverse events that occurred in  $\geq 20\%$  of patients receiving enzalutamide at a rate  $\geq 2$  percentage points higher than that in the placebo group were fatigue, back pain, constipation, and arthralgia. Grade  $\geq 3$  adverse events occurred in 42.9% and 37.1% of the enzalutamide and placebo groups respectively. Serious adverse events occurred in 32.0% and 26.8% of the groups respectively.

## **3. Cost-Effectiveness analysis**

The cost effectiveness of enzalutamide was evaluated using a Markov Model with the states 'Stable', 'Progressed' (subdivided to allow movement to 2<sup>nd</sup> and 3<sup>rd</sup> line treatment and palliative care) and 'Death'. The model has a 10-year time horizon. Cost and benefits are discounted at 5% per annum. The perspective of the evaluation is that of the Health Service Executive under the High Tech Drug Scheme.

The patient level survival curves (overall survival and progression free survival) from the PREVAIL placebo curve (reference arm) were extrapolated using parametric distributions. Hazard ratios were applied to the respective reference curves for the other treatments. Investigator assessed radiographic disease progression data from PREVAIL and COU-AA-302 was used. The Applicant chose this as it was more

mature than the centrally assessed data. Investigator assessed data will be more prone to bias than centrally assessed data.

Data from the placebo arm of PREVAIL (which was more mature than the enzalutamide arm) informed the proportion of patients moving onto 2<sup>nd</sup> line treatment (84.5%). Likewise, data from the placebo arm of PREVAIL informed the proportion moving on to 3<sup>rd</sup> line active treatment (80.9%). The model results are sensitive to both of these inputs.

Frequencies of adverse events for enzalutamide and best supportive care were taken from PREVAIL. Frequencies for abiraterone were taken directly from updated COU-AA-302 data and the abiraterone FDA label. An analysis of comparative safety (enzalutamide vs. abiraterone) was not performed and hence randomisation will be lost. Only Grade  $\geq 3$  adverse events that occurred at an incidence  $\geq 2\%$  in any treatment arm of PREVAIL were included; the model may underestimate the true impact of adverse events. Recent updates to the enzalutamide Summary of Product Characteristics (notably posterior reversible encephalopathy syndrome and hypersensitivity reactions) have not been considered.

The utility and disutility values used in the model were obtained from a range of sources. HRQoL data was collected in PREVAIL using the EQ-5D instrument. The baseline value for all PREVAIL subjects (0.844) was applied to patients in 'Stable'. An on-treatment utility gain (0.022), estimated using the least squares mean estimates, was applied to patients on enzalutamide in 'Stable'. The same gain was assumed for abiraterone. Utility decrements from PREVAIL. No HRQoL data was collected after treatment discontinuation in PREVAIL and therefore literature values were used. The utility values for patients on 2<sup>nd</sup> and 3<sup>rd</sup> line treatments were weighted averages from Wolff *et al* (poster abstract) and Diels *et al*. An on-treatment utility gain (0.06) was estimated from AFFIRM trial data and was applied to patients on enzalutamide post-docetaxel. The same gain was assumed for abiraterone. A utility weight for palliative care (0.5) was derived from Sandblom *et al*. Adverse event disutilities were sourced from the literature.

Costs used in the model include drug acquisition costs, concomitant medications and monitoring. The list price is assumed for abiraterone

### *Results*

The ICER (enzalutamide vs. best supportive care) is €106,271/QALY (incremental cost = €84,634; incremental QALY = 0.796). The ICER (enzalutamide vs. abiraterone) is €74,387/QALY (incremental cost = €25,368; incremental QALY = 0.341). These analyses assume a list price for abiraterone; this may not be realistic.

### *Scenario analysis*

The ICERs are sensitive to the handling of overall survival data. Of particular note:

- If IPCW adjusted data is extrapolated using the Gamma distribution (the preferred distribution according to AIC/BIC) the ICERs increase to €131,587/QALY vs. best supportive care and €136,536/QALY vs. abiraterone.
- If the PREVAIL overall survival data is not adjusted for cross-over the ICERs increase to €125,129/QALY vs. best supportive care and €112,808/QALY vs. abiraterone. If post-enzalutamide treatment with drugs including abiraterone, cabazitaxel and sipuleucic-L (as in PREVAIL) becomes part of clinical practice in Ireland, these ICERs would be more realistic than the basecase ICERs.

The ICERs are less sensitive to the handling of the progression free survival data.

As previously noted, the indirect treatment comparison assumes the comparator arms in both studies to be similar. The model is sensitive to this assumption. The ICER vs. abiraterone falls to €50,242/QALY when abiraterone overall survival and progression free survival data are derived from a naïve indirect treatment comparison.

The Review Group consider the utility value (0.844) applied to the 'Stable' state in the basecase to be relatively high for this population. If this value is decreased to 0.75 (used for a similar patient group in a previous NCPE submission), the ICERs increase to €126,709/QALY vs. best supportive care and €94,342/QALY vs. abiraterone.

### *One-Way Sensitivity analysis*

All parameters were varied in a one way sensitivity analysis. The model was more sensitive to a number of parameters, notably:

- The cost of treatment with enzalutamide or abiraterone.
- The proportions of patients who receive 2nd line treatment and 3rd line treatment
- The hazard ratio for overall survival applied for either enzalutamide or abiraterone
- The discount rates applied to costs and effects
- The model time horizon

#### *Probabilistic analysis*

All model parameters (except drug acquisition costs for enzalutamide and abiraterone) were varied in a probabilistic analysis. At a payer threshold of €45,000/QALY, the probability of enzalutamide (at list price) being cost effective compared to abiraterone (at list price) is 2%, and against best supportive care is 0%.

#### **4. Budget Impact Analysis**

The Budget Impact Model estimates the acquisition cost of treatment with enzalutamide to be about €62,130 per patient (includes mark-ups and High Tech Drug Scheme patient care fee). This estimation assumes that patients are treated with enzalutamide for 16.6 months (median exposure to enzalutamide in PREVAIL). Erroneously, mean durations of treatment were not used in the Budget Impact analysis. The basecase analysis assumes that no discount is applied to either abiraterone or enzalutamide

The basecase 5 year cumulative gross budget impact (enzalutamide acquisition cost) is estimated to be about €71.38 million. The base case net budget impact takes into account the costs of concomitant medications and also of displacing abiraterone (in all eligible patients). Under these assumptions the basecase 5 year cumulative net budget impact is about €12.14 million. The Review Group has run an analysis which assumes that enzalutamide will instead displace best supportive care/abiraterone 50:50. Under this assumption, the 5 year cumulative net impact is €41.76 million.

#### **5. Conclusion**

Astellas Pharma Co Ltd submitted a dossier to examine the cost effectiveness of enzalutamide (Xtandi<sup>®</sup>) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Following

NCPE assessment of the company submission, enzalutamide is not considered cost-effective for this indication and therefore is not recommended for reimbursement at the submitted price.