Cost-effectiveness of enzalutamide (Xtandi®) for the treatment of adults with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high-risk of developing metastatic disease

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of enzalutamide (Xtandi®). Following assessment of the Applicant's submission, the NCPE recommends that enzalutamide (Xtandi®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Astellas) Health Technology Assessment of enzalutamide (Xtandi®). 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 examines all the evidence which 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.

National Centre for Pharmacoeconomics **May 2022**

Summary

In April 2021, Astellas submitted a dossier examining the clinical effectiveness, cost-effectiveness and budget impact of enzalutamide in adults for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high-risk of developing metastatic disease. Castration-resistant prostate cancer (CRPC) is characterised by rising prostate-specific antigen (PSA) levels despite treatment with androgen deprivation therapy (ADT). Treatments for nmCRPC are administered in conjunction with continued ADT. A marketing authorisation was granted by the European Medicines Agency (EMA) for enzalutamide for this indication in October 2018.

Enzalutamide is an androgen receptor inhibitor (ARI). The recommended dose is 160mg (four 40mg tablets) taken orally once daily. Treatment with enzalutamide should continue until disease progression or death. The Applicant is seeking reimbursement under the High-Tech Drug Arrangement.

The reimbursed treatment options in Ireland for nmCRPC are the second-generation ARIs (apalutamide and darolutamide), and ADT. Therefore, apalutamide, darolutamide and ADT are considered as comparators in the cost-effectiveness analysis. Clinical advice gained by the Review Group, indicated combined androgen blockade with bicalutamide may also be considered for older high-risk patients. On request the Applicant also provided a scenario analysis with bicalutamide as a comparator.

1. **Comparative effectiveness of enzalutamide (Xtandi®)**

Direct comparative evidence for the effectiveness of enzalutamide versus ADT in individuals with nmCRPC at high-risk of developing metastases is available from the PROSPER double-blind randomised controlled trial. PROSPER provides the pivotal clinical evidence in the EMA marketing authorisation approval for enzalutamide in nmCRPC.

Individuals were randomised in a 2:1 ratio to receive enzalutamide 160mg orally once daily (n=933) or placebo (n=468); ADT was concomitantly prescribed in both arms. The primary endpoint was metastasis-free survival (MFS) based on blinded independent central review. Secondary endpoints included overall survival (OS), time to PSA progression, time to first

use of new antineoplastic therapy, health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. The first interim analysis (IA1) (June 2017), with a median follow-up of 18.5 months in the enzalutamide group and 15.1 months in the placebo group, provides the final analysis of MFS and the first analysis of OS. The final analysis of OS was conducted in October 2019 with a median follow-up of 48 months. Individuals receiving placebo (n=87) were allowed to crossover to treatment with enzalutamide after study unblinding which occurred at the IA1 analysis.

Median MFS was 36.6 months in individuals receiving enzalutamide and 14.7 months in individuals receiving placebo; hazard ratio (HR) = 0.29 (95% CI 0.24 to 0.35). Median OS was not reached in either treatment arm at the IA1 analysis; HR = 0.80 (95% CI 0.58 to 1.09). At the final analysis median OS was 67.0 months in individuals receiving enzalutamide and 56.3 months in individuals receiving placebo; HR = 0.73 (95% CI 0.61 to 0.89). HRQoL scores indicated that enzalutamide was not detrimental to HRQoL. The Review Group has concerns regarding the immaturity of the trial data. Evidence from international published literature indicates that, in patients with nmCRPC, the median time to development of metastatic CRPC (mCRPC) is approximately five years, with a median survival in mCRPC of up to 19 months. There are also concerns that crossover to enzalutamide in individuals receiving placebo could potentially lead to confounding in long-term survival outcomes. However, it is acknowledged that this is more likely to bias the trial in favour of placebo.

Direct comparative evidence for the effectiveness of enzalutamide versus bicalutamide in individuals with CRPC is available from the STRIVE double-blind randomised controlled trial. The patient population included individuals with both nmCRPC and mCRPC and included low and high-risk disease. STRIVE provides supportive evidence in the EMA marketing authorisation approval of enzalutamide in nmCRPC.

Individuals were randomised in a 1:1 ratio to receive enzalutamide 160mg orally once daily (n=70) or bicalutamide orally 50mg once daily (n=69); ADT was concomitantly prescribed in both arms. The primary endpoint was progression-free survival (PFS). Secondary endpoints included time to PSA progression, radiographic PFS progression-free survival (rPFS), HRQoL outcomes and safety outcomes. A single analysis was performed for the nmCRPC cohort

with a median follow-up of 16.7 months in the enzalutamide group and 16.8 months in the bicalutamide group.

Median PFS was not reached in individuals receiving enzalutamide and was 8.6 months in individuals receiving bicalutamide; HR = 0.24 (95% CI 0.14 to 0.42). The Review Group has concerns regarding the immaturity of the trial data, small patient numbers and the lack of statistical power in the nmCRPC cohort. Further, the eligible population included individuals with low-risk disease; this is not in line with the licensed population.

In the absence of direct head-to-head evidence for the comparisons with apalutamide and darolutamide, a network meta-analysis (NMA) was performed using data from PROSPER and the randomised placebo-controlled SPARTAN and ARAMIS trials of apalutamide and darolutamide, respectively, in individuals with high-risk nmCRPC. All treatments were administered in conjunction with ADT. Overall, the results indicate that enzalutamide has an MFS benefit compared to darolutamide and equivalent MFS to apalutamide. Equivalent OS was demonstrated with enzalutamide and both apalutamide and darolutamide. The Review Group considered the methods used appropriate, notwithstanding some key differences and heterogeneity between the three trials, which may introduce uncertainty and bias. Uncertainty in the results of the NMA will translate into uncertainty in the cost-effectiveness model.

2. **Safety of enzalutamide (Xtandi®)**

The safety analysis included data from the PROSPER trial only. The safety population included all patients who received at least one dose of study treatment. Results are presented for the final analysis, which was used in the cost-effectiveness model. Median treatment exposure was 33.9 months for individuals receiving enzalutamide and 14.2 months for individuals receiving placebo.

Treatment emergent adverse events (TEAEs) were more common in individuals receiving enzalutamide compared to those receiving placebo. The most reported grade 3 or above TEAEs in individuals receiving enzalutamide were hypertension, fatigue, and haematuria.

Serious TEAEs, occurring in at least 1% of individuals receiving enzalutamide, included pneumonia, fall, acute myocardial infarction, anaemia and cardiac failure.

3. **Cost effectiveness of enzalutamide (Xtandi®)**

Methods

The cost-effectiveness of enzalutamide was assessed using a semi-Markov state transition model, with a partitioned survival approach, with a cycle length of one month and a 20-year (lifetime) horizon. A half cycle correction was applied. For each treatment regimen, a hypothetical patient cohort enters the model in the nmCRPC health state; here individuals receive either enzalutamide or comparator treatment and ADT is administered in all treatment arms. Individuals remain in the nmCRPC health state until they experience metastatic progression where they move to the mCRPC health state, where drug treatment for nmCRPC is discontinued. The mCRPC health state is further split into three Markov sub-states (progressed disease [PD] 1 to 3), representing first-, second-, and third-line treatment for mCRPC respectively. Costs of disease management, and utilities differ between the nmCRPC, PD1, PD2 and PD3 health states. A partitioned survival model using the "area under the curve" approach was used to estimate the number of individuals in the nmCRPC and mCRPC health states, using survival curves fitted to the clinical trial data. Transitions between the mCRPC sub-states (PD1 to PD3), based on mean average treatment duration, were informed by the published literature.

Clinical data for enzalutamide versus ADT in the model base case were obtained from the PROSPER trial. The key effectiveness inputs were MFS and OS. Placebo (i.e., ADT) OS data from PROSPER were adjusted for treatment crossover and subsequent treatments (not consistent with those received in clinical practice), using the Inverse Probability of Censoring Weighted method. The adjusted data were used in the model base case of enzalutamide versus ADT. Unadjusted OS data were used for the comparisons with apalutamide and darolutamide. Relative effectiveness (OS and MFS) versus both apalutamide and darolutamide was derived from the NMA. For the comparison with bicalutamide, an MFS treatment effect was derived directly from STRIVE. In the absence of OS data from STRIVE, equal OS (adjusted) was assumed between bicalutamide and ADT.

Each individual health state, including the PD1 to PD3 sub-states, had its own corresponding health state utility value. Event specific disutilities were included for each adverse event and skeletal-related event. An end-of-life utility was also included. The same utility values were used regardless of treatment regimen. Utility values for the nmCRPC and PD1 health states were informed by EQ-5D-5L data (converted to EQ-5D-3L) from PROSPER. Utility values for the PD2 and PD3 health states were informed by key enzalutamide trials in mCRPC.

The Review Group considers that relevant costs were included in the model. Costs were included for drug acquisition (including administration where appropriate), concomitant medication, subsequent treatment, routine care and monitoring, end-of-life care, and the management of TEAEs. Irish cost data were used where available.

Results

The Review Group considered the Applicant's proposed base case to be appropriate, notwithstanding a degree of uncertainty and limitations in some model assumptions. The Review Group had some concerns regarding the method of adjustment for crossover used in the comparison with ADT. The Review Group considered that an alternative method of adjustment (that excluded adjustment for subsequent treatment) would have been less uncertain. An analysis using unadjusted OS for the comparison with bicalutamide was not available. The Applicant incremental cost-effectiveness ratios (ICERs) are shown in Table 1 and the ICER for the comparison with ADT using the NCPE preferred method of OS adjustment is presented in Table 2.

Table 1: Applicant base case analysis*,^,†

Treatment	Total costs (€)	Total QALYS	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Adjusted OS					
Enzalutamide	194,863	4.42			
ADT	93,834	3.30	101,029	1.11	90,709
Bicalutamide	102,106	3.28	92,757	1.14	81,635
Unadjusted OS					
Enzalutamide	193,016	4.29			
Apalutamide	195,173	4.29	-2,156	-1.1×10^{-5}	NA‡
Darolutamide	185,515	4.23	9,501	0.05	179,476

ADT: androgen deprivation therapy; **QALY:** Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio; NA: not applicable; **OS:** overall survival.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable
^Commercial in confidence patient access schemes are in place for apalutamide and darolutamide in nmCRPC and for enzalutamide for mCRPC; these PAS are not included for this analysis.
†All treatments are administered with concomitant ADT.
‡Enzalutamide is less costly than apalutamide with similar effectiveness.

Table 2: NCPE adjusted base case analysis for the comparison with ADT*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Enzalutamide^,†			
ADT	93,235	0.77	120,517

ADT: androgen deprivation therapy; **QALY:** Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable
^A Commercial in confidence patient access schemes is in place for enzalutamide for other indications for which it is reimbursed in Ireland; this PAS is not included for this analysis.
†Enzalutamide is administered with concomitant ADT.

The probability of enzalutamide being cost-effective versus ADT or darolutamide was 0% at thresholds of both €20,000 per QALY and €45,000 per QALY, using the Applicant base case. Enzalutamide is less costly and has a similar effectiveness to apalutamide. The probability of enzalutamide being cost-effective at thresholds of €20,000 per QALY and €45,000 per QALY, compared to ADT, using the NCPE adjusted base case was also 0% for both thresholds. A probabilistic sensitivity analysis was not available for the comparison with bicalutamide.

Deterministic sensitivity analyses, for all comparisons, indicated that model outputs were most sensitive to assumptions surrounding the model fit to MFS curves and the discount rate. The comparison with ADT was also sensitive to assumptions around extrapolation of OS. The comparisons with apalutamide and darolutamide were sensitive to costs associated with the nmCRPC health state, and the choice of effectiveness inputs from the NMA. Deterministic sensitivity analyses were not available for the comparison with bicalutamide.

4. Budget impact of enzalutamide (Xtandi®)

The price to wholesaler of enzalutamide (Xtandi®) is €2,931.19 for a pack of 112 x 40mg tablets. The annual per-patient drug acquisition cost of enzalutamide, including all relevant fees, mark-ups and rebates is €39,936.65 (assuming 100% dose intensity).

The Applicant estimated that 47 individuals would be treated with enzalutamide in year 1, rising to 131 in year 5. The projected cumulative five-year gross drug budget impact of enzalutamide is €19.0 million. The Applicant also presented a net drug budget impact assuming enzalutamide will displace ADT, apalutamide and darolutamide. This resulted in a cumulative five-year net drug budget impact of €7.0 million. Commercial-in-confidence patient access schemes are in place for enzalutamide, apalutamide and darolutamide for currently reimbursed indications; these are not included for this analysis.

Table 3: Drug budget impact of enzalutamide*

Population	Year 1	Year 2	Year 3	Year 4	Year 5	5-year cumulative
Gross drug-budget impact†,‡ (€)	1,883,561	3,407,540	4,755,649	4,730,511	4,254,473	19,031,735
Net drug-budget impact†,‡ (€)	1,429,063	1,804,811	2,051,684	1,214,116	548,557	7,048,232

nmCRPC: non-metastatic castration resistant prostate cancer;
**Including all relevant fees and rebates.*
†*Enzalutamide is an oral treatment; therefore VAT is not applicable.*
‡*Calculations do not include costs of ADT*
A commercial in confidence patient access scheme is currently in place for enzalutamide in mCRPC.

5. Patient submission

No patient organisation submission was received during the course of this assessment.

6. Conclusion

Following assessment of the company submission, the NCPE recommend that enzalutamide (Xtandi®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*