Cost-effectiveness of apalutamide (Erleada®) for the treatment of adults with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of apalutamide (Erleada®). Following assessment of the Applicant's submission, the NCPE recommends that apalutamide (Erleada®) in combination with androgen deprivation therapy be considered for reimbursement if 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 a review of the Applicant's (Janssen Sciences Ireland) Health Technology Assessment of apalutamide (Erleada®). 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 **March 2022**

Summary

In April 2021, Janssen Sciences Ireland submitted a dossier examining the clinical effectiveness, cost-effectiveness, and budget impact of apalutamide in combination with androgen deprivation therapy (ADT) in adults for the treatment of metastatic hormone sensitive prostate cancer (mHSPC). mHSPC (also referred to as metastatic castration-sensitive prostate cancer (mCSPC)) is defined as metastatic prostate cancer sensitive to or not previously treated with hormone therapy (i.e. ADT). mHSPC can either be the initial prostate cancer diagnosis or a relapse from localised disease. The European Medicines Agency granted a licence extension for apalutamide for this indication in January 2020.

Apalutamide is an androgen receptor inhibitor (ARI). The recommended dose is 240mg (four 60mg tablets) taken orally once daily. Treatment with apalutamide should continue until disease progression or death. The Applicant is seeking reimbursement under the High Tech Drug Arrangement.

Another ARI, enzalutamide, has recently received a licence extension for use in mHSPC. Abiraterone acetate in combination with prednisolone (AAP) is licensed for newly diagnosed mHSPC. Neither enzalutamide nor AAP are reimbursed in Ireland for use in mHSPC; enzalutamide is currently under consideration for reimbursement for this indication. Other treatments in Ireland for mHSPC include docetaxel and ADT monotherapy. Therefore, enzalutamide, AAP, docetaxel and ADT are considered as comparators in the cost-effectiveness analysis. Note: all treatments for mHSPC are administered in conjunction with continued ADT.

1. Comparative effectiveness of apalutamide (Erleada®)

Direct comparative evidence for apalutamide versus ADT, in individuals with mHSPC, is available from the TITAN double-blind randomised controlled trial.

Individuals were randomised in a 1:1 ratio to receive apalutamide 240mg once daily (n=525) or placebo (n=527); ADT was concomitantly prescribed in both arms. The dual primary endpoints were radiographic progression-free survival (rPFS) and overall survival (OS).

Secondary endpoints included health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. The first interim analysis (November 2018), with a median follow-up of 22.7 months, provides the final analysis of rPFS and the first analysis of OS. Based on the results of this analysis, the independent data monitoring committee recommended unblinding to allow for the crossover of individuals receiving placebo to open-label apalutamide. Data from the final analysis (September 2020) with 44.0 months of follow up are available.

Median rPFS was not reached in individuals receiving apalutamide plus ADT and was 22.1 months in individuals receiving placebo plus ADT; hazard ratio (HR) = 0.48 (95% CI 0.39 to 0.60). Median OS was not reached in either treatment arm; HR = 0.67 (95% CI 0.51 to 0.89) in the first analysis. At the final analysis, median OS was not reached in individuals receiving apalutamide plus ADT; median OS was 52.2 months in individuals receiving placebo plus ADT; HR = 0.65 (95% CI 0.53 to 0.79). HRQoL scores indicated that apalutamide plus ADT was not detrimental to HRQoL. The NCPE Review Group has concerns regarding the immaturity of the survival data, and that crossover to open label apalutamide plus ADT in individuals receiving placebo plus ADT could potentially lead to confounding in long-term survival outcomes. However, it is acknowledged that this would favour placebo plus ADT.

In the absence of direct head-to-head evidence for the comparisons with enzalutamide, AAP and docetaxel, a network meta-analysis (NMA) was performed using data from TITAN and the randomised-controlled trials ARCHES, CHAARTED, ENZAMET, GETUG-AFU 15 and STAMPEDE (all in individuals with mHSPC). The NMA results suggested that apalutamide had a similar effect on OS compared to AAP and had a numerically favourable effect on OS versus docetaxel and versus enzalutamide; however, no result reached statistical significance. The NMA suggested that apalutamide had a marginally statistically significant rPFS advantage over docetaxel. Enzalutamide and AAP were associated with having a numerically favourable rPFS compared to apalutamide, however neither comparison reached statistical significance. We note that (in the absence of rPFS data for AAP), PFS for AAP was used in the NMA. The Review Group considered the methods used in the NMA appropriate, notwithstanding some key differences and heterogeneity between the trials,

which may introduce uncertainty and bias into the results. Uncertainty in the results of the NMA will translate into uncertainty in the cost-effectiveness model (CEM).

2. Safety of apalutamide (Erleada®)

The safety population of the TITAN trial included all individuals who received at least one dose of study treatment. Results are presented for the final analysis. Median treatment exposure was 39.3 months in individuals receiving apalutamide plus ADT and 20.2 months in those receiving placebo plus ADT.

The occurrence of treatment emergent adverse events (TEAEs) was comparable for both treatments. In the apalutamide plus ADT arm, TEAEs of any grade occurred in 97.3% of individuals; grade 3 to 4 TEAEs occurred in 49.4%. In the placebo plus ADT arm, TEAEs of any grade occurred in 96.8% of individuals; grade 3 to 4 TEAEs occurred in 41.7%. However, apalutamide plus ADT was associated with more drug related TEAEs (any grade (60.9%); grade 3 to 4 (13.9%)) compared to placebo + ADT (any grade (41.9%); grade 3 to 4 (6.1%)). The following grade 3 to 4 TEAEs occurred in more than 2% of individuals receiving apalutamide plus ADT: hypertension (10.3% versus 8.9% in individuals receiving placebo plus ADT), fatigue/asthenia (3.6% versus 1.9%), rash (6.7% versus 0.8%), respiratory, thoracic and mediastinal disorders (4.2% versus 2.3%), general gastrointestinal disorders (excluding diarrhoea) (2.9% versus 1.7%), back pain (2.5% versus 2.9%), and anaemia (2.3% versus 3.6%). Serious adverse events occurred in 29.2% and 21.8% of individuals receiving apalutamide plus ADT and placebo plus ADT respectively.

3. Cost effectiveness of apalutamide (Erleada®)

The cost-effectiveness of apalutamide was assessed using a three-state partitioned survival cost-utility model with a cycle length of one week and a lifetime horizon. A half cycle correction was applied. For each treatment regimen, a hypothetical patient cohort enters the model in the PFS health state; here patients receive either apalutamide or a comparator treatment. Individuals remain in the PFS health state until they experience disease progression to metastatic castrate resistant prostate cancer (mCRPC) where they transition to the post-progression survival (PPS) health state. In the PPS health state, drug treatment for mHSPC is discontinued and individuals can receive up to three lines of subsequent

treatment. It is assumed that all individuals receive ADT until death. Costs of disease management, utilities and risk of death all differ between the PFS and PPS health states. The partitioned survival model uses the "area under the curve" approach, here the number of individuals in each health state at a given time is derived from survival curves fitted to clinical trial data.

Clinical data for apalutamide versus ADT in the model base case were obtained from the TITAN trial. The key effectiveness inputs in the CEM were rPFS, time to treatment discontinuation (TTTD) and OS. OS data from TITAN were adjusted for treatment crossover in the placebo plus ADT arm using a Rank Preserving Structural Failure Time Model. An 'informed fits' approach was taken, in the Applicant base case, using additional clinical data for ADT, with longer follow-up, to inform the OS curves. For the OS and rPFS comparisons with enzalutamide, AAP and docetaxel, HRs from the NMA were applied to reference curves from TITAN. To estimate time to treatment discontinuation (TTTD) for enzalutamide and AAP, rPFS HRs from the NMA were applied to the apalutamide TTTD curve. A fixed treatment duration was assumed for docetaxel.

Utilities identified in the CEM included health state utilities, utility decrements for adverse events, age-related utilities, and an end-of-life utility. Utilities were specific for each treatment arm. Utilities for the PFS and PPS health states were based on EQ-5D-5L data from TITAN. Mapping of EQ-5D-5L to EQ-5D-3L was performed using the van Hout et al cross-walk (2012).

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

Results

The NCPE Review Group considered the Applicant's proposed base case to be appropriate, notwithstanding a degree of uncertainty and limitations in some model assumptions. The incremental cost-effectiveness ratios (ICERs) are shown (Table 1).

Table 1: Applicant base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Apalutamide + ADT^			
ADT	130,838	1.14	114,856
Enzalutamide + ADT^	17,805	0.48	36,739
Docetaxel + ADT	118,097	0.45	263,145
AAP + ADT	2,208	0.02	121,992

AAP: abiraterone acetate in combination with prednisolone; **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.
^ Commercial in confidence patient access schemes are in place for apalutamide and enzalutamide ENZA+ADT for other indications for which they are reimbursed in Ireland; these PAS are not included for this analysis.

The probability of apalutamide being the most cost-effective treatment is presented in Table 2.

Table 2: Probabilities that apalutamide or comparators are the most cost-effective treatments at WTP thresholds of €20,000/QALY and €45,000/QALY.

Treatments	Probability cost-effective at a WTP of €20,000/QALY	Probability cost-effective at a WTP of €45,000/QALY
Apalutamide + ADT vs enzalutamide +ADT		
Apalutamide + ADT	31%	51%
Enzalutamide + ADT	69%	49%
Apalutamide + ADT vs other comparators		
Apalutamide + ADT	0%	0%
ADT	56%	16%
Docetaxel + ADT	44%	84%
AAP + ADT	0%	0%

AAP: *abiraterone acetate plus prednisone;* ***ADT:*** *androgen deprivation therapy;* ***ICER:*** *incremental cost-effectiveness ratio;* ***QALY:*** *quality adjusted life year;* ***WTP:*** *willingness-to-pay.*
Figures in the table are rounded, and so calculations may not be directly replicable.

Deterministic sensitivity analyses indicated that model outputs were most sensitive to assumptions surrounding utilities, the inclusion of a treatment waning effect, compliance rates, HRs for TTTD, rPFS and OS, discount rates, and assumptions regarding subsequent treatments.

4. **Budget impact of apalutamide (Erleada®)**

The price to wholesaler of apalutamide (Erleada®) is €2,978.87 for a pack of 112 x 60mg tablets. The annual per-patient drug acquisition cost of apalutamide, including all relevant fees, mark-ups and rebates is €40,435.29 (assuming 100% dose intensity).

The Applicant estimated that 63 individuals would be treated with apalutamide plus ADT in year 1, rising to 99 in year 5. The projected cumulative five-year gross drug budget impact of apalutamide plus ADT is €38.9 million (of which €38.2 million is for apalutamide).

The Applicant also presented a net drug budget impact assuming apalutamide will displace enzalutamide. This resulted in a cumulative five-year net drug budget impact of €0.6 million. Commercial in confidence patient access schemes are in place for apalutamide and enzalutamide for currently reimbursed indications; these are not included for this analysis.

5. Patient Organisation Submissions

A Patient Organisation Submission was received from Men Against Cancer (MAC). It will be provided to the HSE and form part of the data that the HSE considers.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that apalutamide (Erleada®) in combination with androgen deprivation therapy be considered for reimbursement if 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.