Cost-effectiveness of apalutamide (Erleada®) in adult men for the treatment of 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 apalutamide (Erleada®). Following assessment of the Applicant's submission, the NCPE recommends that apalutamide (Erleada®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Janssen Sciences Ireland UC) economic dossier on the cost effectiveness 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.

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

National Centre for Pharmacoeconomics **August 2020**

Summary

In December 2019, Janssen Sciences Ireland UC submitted a dossier examining the cost-effectiveness of apalutamide in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high-risk of developing metastatic disease. 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 for this indication in January 2019.

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

The only reimbursed treatment options in Ireland for nmCRPC are ADT and secondary hormonal treatments. The use of enzalutamide outside of formal reimbursement (enzalutamide is reimbursed in the metastatic setting) is considered the standard of care in Ireland for patients with high-risk nmCRPC. Therefore, ADT and enzalutamide are considered as comparators in the cost-effectiveness analysis. Darolutamide was granted a licence for use in nmCRPC in January 2020 and therefore may be a potential future comparator.

1. **Comparative effectiveness of apalutamide (Erleada®)**

Direct comparative evidence for the effectiveness of apalutamide versus ADT in patients with nmCRPC at high-risk of developing metastases is available from the SPARTAN double-blind randomised controlled trial.

Patients were randomised in a 2:1 ratio to receive apalutamide 240mg once daily (n=806) or placebo (n=401), with continuous ADT. The primary endpoint was metastasis-free survival (MFS) based on blinded independent central review. Secondary endpoints included overall survival (OS), progression-free survival (PFS), time to metastasis, time to symptomatic

progression, time to initiation of cytotoxic chemotherapy and adverse events (AEs). Health related quality of life (HRQoL) measures were also collected using the Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P) and – General (FACT-G), and the EQ-5D-3L questionnaires. Results from three data-cuts (IA1, IA2 and IA3) are available for the SPARTAN trial. The first interim analysis (IA1) provided the final analysis of MFS, time to metastasis, and PFS. It also provided the first analysis of OS and time to initiation of cytotoxic chemotherapy. The median follow-up at IA1 was 20.3 months. The median follow-up at the time of the second interim analysis (IA2) for OS and time to initiation of cytotoxic chemotherapy was 41 months. The final analysis (IA3) (February 2020) provided the final results for OS. The results of the IA3 final analysis were presented as academic in confidence in the Applicant submission.

Median MFS was 40.5 months in patients receiving apalutamide and 15.7 months in patients receiving placebo; hazard ratio (HR) = 0.30 (95% CI 0.24 to 0.36). At IA1 median OS was not reached in patients receiving apalutamide and was 39.0 months (95% CI 39.0 to not estimable) in patients receiving placebo; HR = 0.70 (95% CI 0.47 to 1.04). It should be noted however that median OS was only reached in patients receiving placebo due to a single event at 39.0 months when there were only two patients at risk. At IA2 median OS was not reached in either treatment arm; HR = 0.75 (95% CI 0.59 to 0.96). HRQoL scores did not indicate a clinically meaningful difference between treatment arms. The Review Group has concerns regarding the relative clinical immaturity of the OS data, such that robust conclusions regarding the relative OS benefit of apalutamide compared to placebo (in conjunction with ADT) cannot be made. 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.

In the absence of direct head-to-head evidence for the comparison with enzalutamide, a matched-adjusted indirect comparison (MAIC) was performed using data from SPARTAN and the randomised-controlled PROSPER trial (enzalutamide plus ADT versus placebo plus ADT in patients with high-risk nmCRPC). Patient-level data from SPARTAN were reweighted to match aggregate data from PROSPER. The Review Group had concerns with the clinical plausibility of the results from the MAIC, as a larger benefit was observed with apalutamide

with OS compared to MFS. This discrepancy is likely due to the immaturity of the OS data in both the SPARTAN and PROSPER trials. Uncertainty with the OS HR will translate into a high level of uncertainty in the cost-effectiveness model.

2. Safety of apalutamide (Erleada®)

The safety population included all patients who received at least one dose of study drug. Results are presented for the IA1 data-cut. Results from subsequent data-cuts did not indicate any major differences. Median treatment exposure was 16.9 months for patients receiving apalutamide and 11.2 months for patients receiving placebo.

AEs were more common in patients receiving apalutamide (any 96.5%; grade ≥3 45.1%) compared to those receiving placebo (any 93.2%; grade ≥3 34.2%). The most commonly reported grade 3-4 AEs in patients receiving apalutamide were hypertension (14.3% vs 11.8% in patients receiving placebo) and skin rash (5.2% vs 0.3% in patients receiving placebo). Frequently reported serious AEs that occurred with a higher incidence in patients receiving apalutamide compared to placebo were fracture (3.4% vs 0.8%, respectively), urinary tract infection (1.2% vs 0.8%), pneumonia (1.1% vs 0.5%) and sepsis (1.0% vs 0%).

3. Cost effectiveness of apalutamide (Erleada®)

Methods

The cost-effectiveness of apalutamide was assessed using a three-state partitioned survival cost-utility model with a cycle length of seven days and a life-time horizon of 30 years. Due to the short length of each model cycle a half cycle correction was not applied. For each treatment regimen, a hypothetical patient cohort enters the model in the nmCRPC health state. Patients remain in the nmCRPC health state until experiencing metastatic progression where they move to the mCRPC health state, where drug treatment for nmCRPC is discontinued and subsequent treatment initiated. ADT is administered continually through the model. Costs of disease management, utilities and risk of death all differ between the nmCRPC and mCRPC health states. The partitioned survival approach uses the “area under the curve” approach, where the number of patients in each health state at a given time is taken directly from survival curves fitted to clinical trial data.

Clinical data for apalutamide (plus ADT) and the comparison with ADT in the model base case was obtained from the SPARTAN trial. The enzalutamide (plus ADT) arm was informed by the clinical evidence from the PROSPER trial. The key effectiveness inputs in the model were MFS, time to treatment discontinuation (TTD) and OS. For the comparison with enzalutamide, HRs from the MAIC were applied to reference curves from SPARTAN.

Utilities identified in the model included health state utilities, a utility for the final 90 days of life and utility decrements for AEs. The same utility values were used regardless of treatment regimen. Utilities for the nmCRPC health state were based on EQ-5D-3L data from SPARTAN. Utilities for mCRPC were sourced from NICE TA387, with the end-of-life utility based on the COU-AA-301 trial in mCRPC. The Review Group considers that relevant costs were included in the model. Costs were included for drug acquisition and administration, costs of handling AEs, medical resource use costs and end-of-life costs. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group suggested several changes to the Applicant base case based on plausible alternative assumptions. These included using the PFS definition from SPARTAN to match the PROSPER MFS definition for the comparison with enzalutamide and using the TTD adjustment for patients discontinuing early and a diminishing treatment effect for both the enzalutamide and ADT comparisons. The NCPE adjusted ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1: NCPE adjusted base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Apalutamide (+ADT) versus ADT	65,555	0.642	102,090
Apalutamide (+ADT) versus Enzalutamide (+ADT)	12,863	0.360	35,741

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

Table 2: Applicant base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Apalutamide (+ADT) versus ADT	65,252	0.700	93,225
Apalutamide (+ADT) versus enzalutamide (+ADT)	12,288	0.406	30,302

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.

The probabilistic sensitivity analysis using the NCPE adjusted base case model gave similar results to the deterministic model. The probability of apalutamide (plus ADT) being cost-effective was estimated at 0% at a threshold of €20,000 per QALY and 0.2% at a threshold of €45,000 per QALY, for the comparison with ADT. In the comparison with enzalutamide (plus ADT) the probability of apalutamide (plus ADT) being cost-effective was estimated at 22.7% at a threshold of €20,000 per QALY and 59.0% at a threshold of €45,000 per QALY. The Review Group had concerns that all comparisons were associated with a high degree of uncertainty.

Many scenario analyses were presented addressing structural uncertainty and model assumptions. The scenarios that had the largest effect on the results were the extrapolation curves used in MFS and OS, treatment duration assumptions, treatment waning, and subsequent treatment distribution and duration. ICERs ranged from €19,590 (exponential distribution for OS) to €135,264 (generalised gamma distribution for MFS) per QALY for the

NCPE adjusted comparison with ADT and from apalutamide being dominated (exponential distribution for OS) to €47,945 (subsequent treatment distribution taken from SPARTAN) per QALY for the comparison with enzalutamide (plus ADT).

4. Budget impact of apalutamide (Erleada®)

The price to wholesaler of apalutamide is €2,978.87 for a pack of 112 x 60mg tablets. The annual drug acquisition cost of apalutamide, including all relevant fees, mark-ups and rebates is €40,435 per patient; assuming 100% dosing intensity.

The Applicant estimated that 21 patients would be treated with apalutamide in year 1, rising to 40 in year 5. The Review Group had some concern regarding the estimation of eligible patient numbers and that the potential budget impact may be underestimated. It is however recognised that published information on the frequency and characteristics of patients with CRPC is lacking and there is significant uncertainty around the number of patients with nmCRPC in Ireland. The projected cumulative 5-year gross budget impact of apalutamide (plus ADT) is €7.2 million.

The Applicant also presented a net budget impact assuming apalutamide will displace enzalutamide. This resulted in a cumulative 5-year net budget impact of €71,254. However, there is a confidential patient access scheme in place for enzalutamide. Therefore, the actual net budget impact is underestimated.

5. Patient Submission

No patient submissions were received in support of the application.

6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that apalutamide for the treatment of nmCRPC in patients at high risk of metastasis 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.