Cost-effectiveness of darolutamide (Nubeqa®) for the treatment of adult men 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 darolutamide (Nubeqa®). Following assessment of the Applicant's submission, the NCPE recommends that darolutamide (Nubeqa®) 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 a review of the Applicant's (Bayer) Health Technology Assessment of darolutamide (Nubeqa®). 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 **September 2021**

Summary

In December 2020, Bayer submitted a dossier examining the clinical effectiveness, cost-effectiveness and budget impact of darolutamide in adult men 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 for darolutamide for this indication in March 2020.

Darolutamide is an androgen receptor inhibitor (ARI). The recommended dose is 600mg (two 300mg tablets) taken orally twice daily. Treatment with darolutamide 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 ADT and secondary hormonal treatments. Two other ARIs, apalutamide and enzalutamide, are licensed but are not reimbursed for use in nmCRPC. A full HTA of enzalutamide is currently ongoing and apalutamide is currently under consideration for reimbursement for patients with high-risk nmCRPC. Therefore, ADT is considered the primary comparator with apalutamide and enzalutamide considered secondary comparators in the cost-effectiveness analysis.

1. Comparative effectiveness of darolutamide (Nubeqa®)

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

Patients were randomised in a 2:1 ratio to receive darolutamide 600mg twice daily (n=955) or placebo (n=554); ADT was concomitantly prescribed in both arms. The primary endpoint was metastasis-free survival (MFS) based on blinded independent central review (BICR). Secondary endpoints were evaluated in a hierarchical order; overall survival (OS), time to

pain progression, time to first cytotoxic chemotherapy and time to first symptomatic skeletal event (SSE) were tested sequentially. Progression-free survival (PFS) and health related quality of life (HRQoL) outcomes (including EQ5D-3L) were exploratory endpoints. The primary analysis (September 2018) provided the final analysis of MFS and time to pain progression and the interim analysis of OS, time to first cytotoxic chemotherapy and time to first SSE. As the primary endpoint (MFS) was statistically significant, unblinding of treatment assignments occurred (November 2018), and patients in the placebo plus ADT group were permitted to cross-over to receive open-label darolutamide plus ADT. The final analysis for OS, time to f first cytotoxic chemotherapy and time to first SSE took place in November 2019. Assessments by BICR were not carried out after unblinding. The median follow-up at the time of the primary analysis was 17.9 months and 29.0 months at the final analysis.

Baseline scans were re-analysed by BICR and identified 89 patients as being misclassified as metastasis-free at baseline. These patients were included in the primary analyses of MFS, with baseline metastasis counted as an event at day zero (BME), however, an additional sensitivity analysis was conducted with baseline metastases censored (BMC). Median MFS (BME) was 40.4 months in patients receiving darolutamide plus ADT and 18.4 months in patients receiving placebo plus ADT; hazard ratio (HR) = 0.41 (95% CI 0.34 to 0.50). Median MFS (BMC) was 40.5 months in patients receiving darolutamide plus ADT and 22.1 months in patients receiving placebo plus ADT; HR = 0.36 (95% CI 0.29 to 0.44). Median OS was not reached in either treatment arm at the primary or final analysis; HRs = 0.71 (95% CI 0.50 to 0.99) and 0.69 (95% CI 0.53 to 0.88), respectively. HRQoL scores indicated that darolutamide was not detrimental to HRQoL. The Review Group has concerns regarding the clinical immaturity of the OS data, such that robust conclusions regarding the relative OS benefit of darolutamide plus ADT compared to placebo plus ADT cannot be made. 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.

In the absence of direct head-to-head evidence for the comparisons with apalutamide and enzalutamide, a network meta-analysis (NMA) was performed using data from ARAMIS and the randomised-controlled SPARTAN and PROSPER trials of apalutamide plus ADT and

enzalutamide plus ADT, respectively, versus placebo plus ADT in patients with high-risk nmCRPC. The Review Group considered the methods used appropriate, notwithstanding some key differences and heterogeneity between the three trials, which may introduce uncertainty and bias into the results. Uncertainty in the results of the NMA will translate into a high level of uncertainty in the cost-effectiveness model.

2. Safety of darolutamide (Nubeqa®)

The safety population of the ARAMIS trial included all patients who received at least one dose of study treatment. Results are presented for the primary analysis, i.e. the double-blind phase of the trial, as this data was used in the cost-effectiveness model. Median treatment exposure was 14.8 months for patients receiving darolutamide and ADT and 11.0 months for patients receiving placebo plus ADT. Results from the final analysis and for patients crossing-over from placebo plus ADT to darolutamide plus ADT did not indicate any notable differences in the pattern of AEs.

Adverse events (AEs) were more common in patients receiving darolutamide plus ADT (any 83.2%; grade ≥3 24.7%) compared to those receiving placebo plus ADT (any 76.9%; grade ≥3 19.5%). The most reported grade 3 to 4 AEs in patients receiving darolutamide plus ADT were hypertension (3.1% vs 2.2% in patients receiving placebo plus ADT), coronary-artery disorder (1.7% vs 0.4%) and urinary retention (1.6% vs 2.0%). Serious AEs occurring in at least 1% of patients receiving either darolutamide plus ADT or placebo plus ADT, respectively, were urinary retention (1.6% vs. 3.2%), pneumonia (1.4% vs. 1.1%) and haematuria: (1.0% vs. 1.1%).

3. Cost effectiveness of darolutamide (Nubeqa®)

Methods

The cost-effectiveness of darolutamide was assessed using a three-state partitioned survival cost-utility model with a cycle length of 28 days and a life-time horizon. A half cycle correction was applied. For each treatment regimen, a hypothetical patient cohort enters the model in the nmCRPC health state; here patients receive either darolutamide plus ADT or comparator plus ADT. Patients 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 and patients can receive up to three lines of subsequent treatment. Costs of disease management, utilities and risk of death all differ between the nmCRPC and mCRPC health states. The partitioned survival model 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 darolutamide plus ADT and the comparison with ADT in the model base case were obtained from the ARAMIS trial. The apalutamide plus ADT and enzalutamide plus ADT comparisons were informed by the clinical evidence from the SPARTAN and PROSPER trials, respectively. The key effectiveness inputs in the model were MFS, time on treatment (ToT) and OS. For the comparisons with apalutamide and enzalutamide, HRs from the NMA were applied to reference curves from ARAMIS for MFS and OS, with ToT assumed to equal that of darolutamide.

Utilities identified in the model included health state utilities and utility decrements for AEs. The same utility values were used regardless of treatment regimen. The utility for the nmCRPC health state was based on EQ-5D-3L data from ARAMIS. The utility for the mCRPC health state were sourced from the external literature. To capture the QALYs associated with the different lines of subsequent treatment a weighted average utility was estimated based on the average time spent in each line of therapy (sourced from NICE TA377 for enzalutamide in mCRPC) and utilities used in NICE TA580 (for enzalutamide in nmCRPC).

The Review Group considers that relevant costs were included in the model. Costs were included for drug acquisition (including administration), subsequent treatment, monitoring, end-of-life care and the management of AEs and SSEs. Healthcare resource use assumptions and utilisation for the nmCRPC and mCRPC states were based on NICE TA580 and NICE TA377 estimates. 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 assuming equal effectiveness of darolutamide, apalutamide

and enzalutamide, equal mortality of darolutamide and ADT after five years and the assumption of different utilities in the mCRPC health state for different treatment arms. The NCPE adjusted incremental cost effectiveness ratios (ICERs) (Table 1) and the Applicant ICERs (Table 2) are shown.

Table 1: NCPE adjusted base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Darolutamide plus ADT			
ADT†	89,975	0.83	129,510
Apalutamide plus ADT	-715	0.0007	Darolutamide dominates
Enzalutamide plus ADT	37	0.0013	28,921

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
†Primary comparator

Table 2: Applicant base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Darolutamide plus ADT			
ADT†	72,932	1.31	55,785
Apalutamide plus ADT	-1,178	0.21	Darolutamide dominates
Enzalutamide plus ADT	-860	0.07	Darolutamide dominates

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
†Primary comparator

The probability of darolutamide being cost-effective versus ADT was 0% at thresholds of €20,000 per QALY and €45,000 per QALY, using the NCPE adjusted base case. For the comparison with apalutamide, the probability of darolutamide being cost-effective was 55% for both the €20,000 per QALY and €45,000 per QALY thresholds. For the comparison with enzalutamide, the probability of darolutamide being cost-effective was 52% for both the €20,000 per QALY and €45,000 per QALY thresholds. All comparisons were associated with a high degree of uncertainty.

Deterministic sensitivity analyses indicated that the NCPE adjusted base case was most sensitive to assumptions surrounding utilities in the nmCRPC health state in the comparison with ADT and subsequent treatment costs in the comparisons with apalutamide and enzalutamide.

4. Budget impact of darolutamide (Nubeqa®)

The price to wholesaler of darolutamide is €2,957.62 for a pack of 112 x 300mg tablets. The annual per-patient drug acquisition cost of darolutamide, including all relevant fees, mark-ups and rebates is €40,290 (assuming 100% dose intensity).

The Applicant estimated that 18 patients would be treated with darolutamide in year 1, rising to 45 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 uncertainty around the number of patients with nmCRPC in Ireland. The projected cumulative five-year gross budget impact of darolutamide alone is €6.3 million.

The Applicant also presented a net budget impact assuming darolutamide will displace apalutamide and enzalutamide. This resulted in a cumulative five-year net budget saving of €22,242. However, there is a confidential Patient Access Scheme in place for enzalutamide for the metastatic CRPC indication. Therefore, the actual net budget impact is underestimated.

5. Patient Submission

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

Given that ADT is the primary comparator, following assessment of the company submission, the NCPE recommend that darolutamide (Nubeqa®) 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.