NCPE Assessment

Summary Report

Capivasertib (Truqap®)

24015

26 March 2026

Applicant: AstraZeneca Pharmaceutical (Ireland) DAC

Capivasertib in combination with fulvestrant for the treatment of adult patients with oestrogen receptor positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer with *PIK3CA/AKT1/PTEN*-alteration following recurrence or progression on or after an endocrine-based regimen.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of capivasertib (Truqap®) (when given in combination with fulvestrant) for the treatment of adult patients with oestrogen receptor positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer with *PIK3CA/AKT1/PTEN*-alteration following recurrence or progression on or after an endocrine-based regimen.

Following assessment of the Applicant's submission, the NCPE recommends that capivasertib (Truqap®) (when given in combination with fulvestrant) not be considered for reimbursement for this indication, unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca Pharmaceutical (Ireland) DAC) Health Technology Assessment of capivasertib (Truqap®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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.

Summary

In June 2025, AstraZeneca Pharmaceutical (Ireland) DAC submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of capivasertib (Truqap®) for the treatment of adult patients with oestrogen receptor positive (ER-positive), human epidermal growth factor receptor 2-negative (HER2-negative), locally advanced or metastatic breast cancer (mBC) with *PIK3CA/AKT1/PTEN*-alteration following recurrence or progression on or after an endocrine-based regimen. Reimbursement is being sought under the High-Tech (HT) Drug Arrangement. Capivasertib is an oral, highly potent, ATP-competitive inhibitor that acts by binding to AKT, preventing its phosphorylation and subsequent activation, which shuts down the *PI3K/AKT/PTEN* signalling pathway and inhibits tumour cell proliferation, survival, and growth, particularly in tumours with *PIK3CA/AKT1/PTEN* alterations. Fulvestrant is a selective oestrogen receptor degrader that acts as a pure anti-oestrogen to treat ER-positive mBC by binding to, blocking, and degrading oestrogen receptors. The recommended dose of capivasertib is 400mg (2 x 200mg tablets orally) twice daily, for four days followed by three days off treatment (weekly cycles). The recommended dose of fulvestrant is 500mg (administered via two 250mg intramuscular injections) on Days 1, 15, and 29, and once monthly thereafter. Treatment with capivasertib in combination with fulvestrant should be continued until disease progression or unacceptable toxicity occurs.

The current standard of care (SoC) for patients with locally advanced or mBC for most patients is endocrine therapy (ET) plus a cyclin-dependent kinase (CDK) 4/6 inhibitor. Most patients who progress to second-line treatment receive fulvestrant monotherapy, everolimus plus exemestane, or everolimus monotherapy. The Applicant suggests that capivasertib plus fulvestrant will be used as a second-line treatment option for patients whose disease has recurred or progressed following first-line treatment with an ET-based regimen and a CDK4/6 inhibitor. This is narrower than the full licensed population however, clinical opinion to the Review Group indicated this to be the expected place in therapy for capivasertib, if reimbursed. The Review Group note that alpelisib plus fulvestrant is licensed but not reimbursed at this time for patients with a *PIK3CA* mutation and may be a relevant comparator in the future in patients with a *PIK3CA* mutation. Inavolisib (plus palbociclib and fulvestrant) underwent a NCPE Rapid Review appraisal in September 2025; a full HTA is

recommended.

1. Comparative effectiveness of capivasertib

The efficacy and safety of capivasertib plus fulvestrant was assessed in the CAPItello-291 trial. CAPItello-291 is an ongoing phase III, randomised, double-blind, placebo-controlled trial comparing the efficacy of capivasertib plus fulvestrant versus placebo (plus fulvestrant), in participants with ER-positive, HER2-negative advanced or mBC whose disease progressed during or after ET, with or without a CDK4/6 inhibitor. Capivasertib plus fulvestrant, and placebo (plus fulvestrant) were administered as per the SmPC dosing. The co-primary endpoints were investigator-assessed progression-free survival (PFS) per RECIST in the overall trial population, and in the *PIK3CA/AKT1/PTEN*-altered subpopulation. Overall survival (OS) was a key secondary endpoint.

The results presented here are those in the *PIK3CA/AKT1/PTEN*-altered subpopulation who have received prior ET and prior CDK4/6 inhibitor treatment (i.e. a subpopulation of the full licensed population which stipulates prior ET treatment only). In the final PFS analysis (data cut-off 1 [DCO1], 15 August 2022) median PFS was 5.5 months (95% confidence interval [CI] 3.9 to 7.4 months) in the capivasertib plus fulvestrant arm and 2.0 months (95% CI 1.8 to 3.1 months) in the placebo plus fulvestrant arm. The hazard ratio (HR) was 0.46 (95% CI 0.34 to 0.63). OS was derived from interim DCO2 (15 April 2024), where the median OS was 28.1 months (95% CI 20.4 to 32.9 months) in the capivasertib plus fulvestrant arm and 21.2 months in the placebo plus fulvestrant arm (95% CI 14.3 to 30.6 months). The HR was 0.80 (95% CI 0.57, 1.13). Global health status and quality of life were maintained in both the capivasertib plus fulvestrant arm and the placebo plus fulvestrant arm and maintained for longer with capivasertib plus fulvestrant than with placebo plus fulvestrant. Limitations of CAPItello-291 include: that a statistically significant OS benefit has not been demonstrated for capivasertib plus fulvestrant versus placebo plus fulvestrant in DCO2 (interim OS analysis); and the CDK4/6 inhibitor-naïve participants in CAPItello-291 (29%) are not reflective of the population expected to receive capivasertib plus fulvestrant in Ireland (i.e., patients with prior CDK4/6 inhibitor treatment).

CAPItello-291 provided head-to-head comparative efficacy data for capivasertib plus fulvestrant versus fulvestrant monotherapy. Head-to-head evidence for capivasertib plus fulvestrant versus exemestane monotherapy, and versus everolimus plus exemestane was

not available and a network meta-analysis (NMA) was required. The Applicant's NMA compared PFS and OS between capivasertib plus fulvestrant (from CAPItello-291, and a UK-based phase II trial FAKTION), and seven other trials (FAKTION, BOLERO-2, BOLERO-5, EFECT, SOFEA, CONFIRM, FRIEND and NCT01300351) including exemestane monotherapy, everolimus plus exemestane, and fulvestrant as treatments. A time-varying HR approach was chosen by the Applicant which assumes that the HR between the treatments changes over time. Fulvestrant monotherapy was considered the reference treatment. The Applicant stated that the evidence of violation of proportional hazards is modest and limited to the early period of follow-up, and that the use of constant HR over time would provide the most robust basis for estimation of event rates for comparators. A constant (fixed) HR for the NMA was instead implemented for the NCPE adjusted base case. In the NMA, a PFS benefit in terms of median PFS for capivasertib plus fulvestrant was observed versus fulvestrant monotherapy, everolimus plus exemestane, and exemestane monotherapy, in the time period between 0 and three months, but not beyond three months. For OS, no statistically significant benefit was observed for capivasertib plus fulvestrant versus exemestane monotherapy, everolimus plus exemestane and fulvestrant monotherapy at 0 to six months, but not beyond six months. Limitations of the NMA include that the majority of studies (8 out of 9) did not include patients with prior CDK3/6 inhibitor treatment, and *PIK3CA/AKT1/PTEN* alteration status was unknown in 7 out of 9 studies.

2. Safety of capivasertib

The safety population in CAPItello-291 included 355 patients who received capivasertib plus fulvestrant and 350 patients who received placebo plus fulvestrant. The most common adverse events (AEs) of any grade that were reported in the capivasertib plus fulvestrant arm were diarrhoea (72.4% versus 20.6% in the placebo plus fulvestrant arm), rash (22.3% versus 5.1%), and nausea (34.6% versus 16.3%). Hyperglycaemia of any grade occurred in 17.2% of the participants who received capivasertib plus fulvestrant and in 3.7% of those who received placebo plus fulvestrant. The safety profile of capivasertib plus fulvestrant in the subgroup with altered AKT pathway was similar to that in the overall trial population. Serious adverse events (SAEs) occurred in 18.0% of participants receiving capivasertib plus fulvestrant and in 8.6% receiving placebo plus fulvestrant, including diarrhoea (2.5%), rash (1.4%), and vomiting (1.1%). The incidence of AEs of Grade 4 was

3.4%. The SmPC carries special warnings for hyperglycaemia, diarrhoea, rash and other skin drug reactions.

3. Cost effectiveness of capivasertib

The Applicant has compared the cost-effectiveness of capivasertib plus fulvestrant, to fulvestrant monotherapy, exemestane monotherapy and everolimus plus exemestane in the base case.

Methods

The cost-effectiveness model (CEM) is a partitioned survival model with three health states: Progression Free [PF], Progressed Disease [PD], and Death. These health states capture PFS and OS. The model had a horizon of 30 years and the cycle length was one month. The population was modelled based on the CAPItello-291 trial *PIK3CA/AKT1/PTEN*-altered subpopulation. All patients enter the model in the PF health state and receive treatment with either capivasertib plus fulvestrant, fulvestrant monotherapy, or exemestane monotherapy. During each model cycle, patients can transition from the PF health state to the PD health state or Death health state or remain in the PF health state. Following disease progression, patients cannot transition back to improved health states and can either remain in the PD health state or transition to the Death health state. In each cycle, patients accrue quality adjusted life years (QALYs) and incur costs based on their health state, treatment arm, and time on treatment (ToT).

For both PFS and OS, the Applicant chose a parametric survival distribution for the fulvestrant arm and applied a HR from the NMA to model all other comparators, including capivasertib plus fulvestrant (relative efficacy assumption). Therefore, full Kaplan-Meier data from the capivasertib plus fulvestrant arm from CAPItello-291 is not utilised in the Applicant's base case. In the NCPE adjusted base case, data from both arms of CAPItello-291 were used to inform the modelling of fulvestrant and capivasertib plus fulvestrant for both PFS (using an independent fit assumption) and OS (using a joint fit assumption).

The ToT with fulvestrant, in the CEM, was estimated by extrapolation of data from the CAPItello-291 trial (ToT for placebo plus fulvestrant). Data from CAPItello-291 was not used to directly inform ToT with capivasertib plus fulvestrant, instead a HR was estimated for the relationship between ToT and PFS for capivasertib plus fulvestrant and applied to the PFS

curve to estimate ToT. The same approach was applied to the estimation of ToT for everolimus plus exemestane and exemestane monotherapy in the absence of data on ToT. The Review Group accepted this approach. However, we note that this implies a shorter mean duration of treatment than the mean intended duration of treatment observed in the trial and therefore this may underestimate the ICER. Additionally, the Review Group note that the HR between PFS and ToT in CAPItello-291 decreased over time and therefore used a lower HR than the Applicant from 18 months onwards.

Results

An incremental analysis of the costs and benefits of capivasertib plus fulvestrant versus fulvestrant monotherapy, exemestane monotherapy and everolimus plus exemestane was presented by the Applicant. The probabilistic results, which were estimated for 1,000 simulations, are stable and similar to the deterministic results.

Table 1: Applicant base case incremental cost-effectiveness results [a]

			Capivasertib + fulvestrant vs		
Treatments	**Total costs (€)**	**Total QALYs**	**Incremental costs (€)**	**Incremental QALYs**	**ICER (€/QALY)**
Capivasertib + fulvestrant	112,530	2.23	-	-	-
Fulvestrant	62,772	1.78	49,758	0.45	111,429
Everolimus + exemestane	69,664	1.68	42,866	0.55	78,523
Exemestane	59,189	1.51	53,341	0.72	73,648

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year.

[a] Corresponding probabilistic ICER using 1,000 iterations =€114,243/QALY (versus fulvestrant), =€81,110/QALY (versus everolimus + exemestane), =€73,752/QALY (versus exemestane). Figures in the table are rounded, and so calculations may not be directly replicable. Costs and outcomes are discounted at a rate of 4.0%.

The Review Group assessment identified a number of limitations in the Applicant's base case which were explored in the NCPE adjusted base case. These included: model type (joint fit, independent fit, relative effectiveness), choice of OS extrapolation curve, alteration test costs, relative dose intensity, subsequent treatments, HR for the NMA (fixed, time-varying) and ToT.

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a]

			Capivasertib + fulvestrant vs		
Treatments	**Total costs (€)**	**Total QALYs**	**Incremental costs (€)**	**Incremental QALYs**	**ICER (€/QALY)**
Capivasertib + fulvestrant	124,770	2.05			
Fulvestrant	58,298	1.69	66,472	0.35	189,041

Everolimus + exemestane	70,484	1.57	54,286	0.48	114,083
Exemestane	54,960	1.42	69,810	0.63	110,782

ICER: incremental cost-effectiveness ratio; **NCPE**: National Centre for Pharmacoeconomics; **QALY**: quality adjusted life year.
a Corresponding probabilistic ICER using 1,000 iterations =€194,336/QALY (versus fulvestrant), =€117,967/QALY (versus everolimus + exemestane), =€112,109/QALY (versus exemestane). Figures in the table are rounded, and so calculations may not be directly replicable. Costs and outcomes are discounted at a rate of 4.0%.

Sensitivity analysis

In the NCPE-adjusted base case, capivasertib plus fulvestrant has a 0% probability of cost effectiveness at the 20,000/QALY threshold versus all comparators. Capivasertib plus fulvestrant has a 0.1% probability, a 1.5% probability, and a 0.2% probability of cost effectiveness at the 45,000/QALY threshold versus fulvestrant monotherapy, versus everolimus plus exemestane, and versus exemestane monotherapy, respectively. A Price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that a 93%, 64% and 78% reduction in the price-to-wholesaler (PtW) of capivasertib was required to meet the €45,000 per QALY threshold when compared to fulvestrant monotherapy, versus everolimus plus exemestane, and versus exemestane monotherapy respectively. At the €20,000 per QALY threshold cost-effectiveness could not be achieved at any price versus fulvestrant monotherapy and exemestane monotherapy, and an 83% price reduction was required versus everolimus plus exemestane.

4. Budget impact of capivasertib

The PtW of capivasertib is €6,500 per pack (64 x 200mg tablets). The PtW for fulvestrant is €129.51 per pack (250mg, 2x5ml pre-filled syringes). The estimated cost of capivasertib plus fulvestrant per-patient, per-treatment course is €62,695 (including VAT), assuming a mean treatment duration of 8.63 months derived from the NCPE-adjusted base case CEM. The Applicant's estimated gross and net drug budget impact estimates were considered very uncertain, and a NCPE adjusted budget impact model is presented with the following changes: a 100% testing rate for the *PIK3CA/AKT1/PTEN* alteration was applied; an RDI of 100% assumed; and treatment duration as predicted by the NCPE-adjusted base case CEM was applied. Market share changes and cost corrections were also made. The NCPE adjusted five-year gross drug budget impact estimate for capivasertib plus fulvestrant is €43.7 million (including VAT) and the cumulative five-year net drug-budget impact estimate is €37.9

million (including VAT). The product licence does not restrict use of capivasertib plus fulvestrant to patients who are previously treated with CDK4/6 inhibitors. A scenario that removed this assumption, resulted in a net drug budget impact to €39.9 million (including VAT). In a scenario which applied the mean intended duration of treatment at DC02 from CAPItello-291 (10 months for capivasertib, 10.65 months for fulvestrant in the capivasertib plus fulvestrant arm, and 6.81 months of fulvestrant monotherapy in the placebo plus fulvestrant arm), and the mean duration of treatment observed in BOLERO-2 (7.2 months for everolimus, 7.84 months for exemestane in the everolimus plus exemestane regimen, and 4.93 months of exemestane monotherapy), the net drug-budget impact increased to €44.4 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that capivasertib plus fulvestrant not be considered for reimbursement unless cost-effectiveness can be improved*.

*Next steps: The NCPE Assessment Report and recommendation, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. Further information on this process may be found here.