Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2930

capivasertib film-coated tablet (Truqap®)

AstraZeneca UK

07 August 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the end of life and orphan equivalent medicine process

capivasertib (Truqap®) is accepted for restricted use within NHSScotland.

Indication under review: in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen.

SMC restriction: restricted to patients whose disease has progressed following CDK4/6 inhibitor plus aromatase inhibitor therapy.

Evidence from a double-blind, phase III study, demonstrated that addition of capivasertib to fulvestrant significantly improved progression-free survival (PFS) but not overall survival (OS). An indirect comparison suggested no difference in these outcomes between capivasertib-fulvestrant and everolimus-exemestane.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Capivasertib inhibits kinase activity of all isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). AKT is pivotal in phosphatidylinositol-3-kinase (PI3K) signalling, which contributes to cell survival, proliferation and migration. AKT can be activated in breast cancers due to mutations of AKT or PI3K catalytic subunit (PI3KCA) or loss of Phosphatase and Tensin Homolog (PTEN) function. Capivasertib reduces growth of these cancer cells and combining it with fulvestrant gives a greater anti-tumour response. Capivasertib is given orally in weekly cycles (400 mg twice daily for 4 days, then 3 days off treatment) in combination with fulvestrant (500 mg intramuscularly [IM] on Days 1, 15, and 29 then every 28 days) and continued until disease progression or unacceptable toxicity. See summary of product characteristics for more information.[1]

1.2. Disease background

Locally advanced or metastatic breast cancer is an incurable disease, comprising a variety of subtypes defined by molecular markers. Approximately 70% of breast cancers are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative, with approximately half of these having overactivation of the PI3K-AKT-PTEN signalling pathway due to activating mutations in PIK3CA and AKT1 and inactivating alterations in PTEN. Systemic treatment aims to prolong survival, alleviate symptoms, and maintain or improve quality of life.[2, 3]

1.3. Company proposed position

The company has requested that SMC considers capivasertib when positioned for use in the licensed indication for patients whose disease has progressed following CDK4/6 inhibitor plus aromatase inhibitor therapy.

1.4. Treatment pathway and relevant comparators

Standard first-line therapy for HR-positive, HER2-negative metastatic breast cancer is a CDK4/6 inhibitor (abemaciclib, palbociclib or ribociclib) plus endocrine therapy. The latter can include an aromatase inhibitor (steroidal: exemestane; non-steroidal: letrozole or anastrozole) for patients who have not relapsed on or within 12 months of stopping adjuvant aromatase inhibitor therapy, or with fulvestrant (a selective oestrogen receptor degrader [SERD]) for those who have. Patients who have rapid progression should be considered for chemotherapy with or without maintenance endocrine monotherapy. In those with a good initial response, the optimal sequence of subsequent therapy is uncertain, and it is individualised. Some patients choose single-agent chemotherapy (such as capecitabine or paclitaxel) while others continue with second-line endocrine based therapy. The mammalian target of rapamycin (mTOR) inhibitor, everolimus, can be used in this setting, and is accepted by SMC (advice 872/13) for use in combination with exemestane in post-menopausal women who have disease recurrence or progression following a non-steroidal aromatase inhibitor. Alpelisib, an α-specific class I (PI3Kα) inhibitor, is licensed for second-line use after endocrine based therapy, in combination with fulvestrant for patients with PIK3CA mutations. However, SMC published advice (SMC2481) in December 2022, that it is not recommended for use within NHS Scotland for this indication. Fulvestrant monotherapy is another treatment option following disease relapse or disease progression on anti-oestrogen therapy

(SMC114/04).[4, 5] Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data indicate that following a CDK4/6 inhibitor plus endocrine therapy for HR-positive, HER2-negative advanced breast cancer, most patients who then received a systemic anti-cancer therapy (that is, excluding those who had endocrine monotherapy e.g. fulvestrant monotherapy) had capecitabine or to a lesser extent paclitaxel monotherapy ; a small proportion received everolimus with or without exemestane .[6]

The submitting company considers fulvestrant monotherapy and everolimus-exemestane to be the main comparators, with capecitabine considered in an economic scenario analysis.

1.5. Category for decision-making process

Eligibility for interim acceptance decision option

Capivasertib has received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway (ILAP).

Eligibility for a PACE meeting

Capivasertib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Clinical evidence is from the CAPItello-291 study, detailed in Table 2.1.[2]

Table 2.1. Overview of relevant studies.[2]

Criteria	CAPItello-291
Study design	Double-blind, international, phase III study.
Eligible patients	Pre-, peri- or post-menopausal adults (age ≥18 years; ≥20 years in Japan) with HR-positive, HER2-negative locally advanced (inoperable) or metastatic breast cancer who have disease recurrence or progression on or after an aromatase inhibitor. They had ECOG or WHO performance status 0 or 1, and measurable disease per RECIST v1.1 or ≥1 lesion or bone lesion assessed by CT or MRI scan.
Treatments	Patients were equally assigned to a weekly schedule: capivasertib 400 mg twice daily for four days followed by three days off treatment or placebo. All patients received fulvestrant 500 mg IM on Day 1, 15 and 29, then every 28 days. Study treatment continued until disease progression or unacceptable toxicity. Pre- or peri-menopausal women received LHRH agonist for all the treatment period.
Randomisation	Randomisation was stratified by liver metastases (yes or no), prior CDK4/6 inhibitor (yes or no) and location (United States, Canada, Western Europe, Australia and Israel or Latin America, Eastern Europe and Russia or Asia).
Primary outcome	The co-primary outcomes were investigator-assessed PFS, defined as the time from randomisation to progression on RECISTv1.1 or death from any cause in the total study population, which comprised all randomised patients, and in the subgroup with PIK3CA/AKT1/PTEN-altered tumours (the 'altered population').
Key secondary outcomes	OS, defined as the time from randomisation to death from any cause. ORR, defined as CR or PR on RECISTv1.1.
Statistical analysis	The co-primary outcomes and OS were controlled for multiplicity.

Abbreviations: AKTI = AKT serine/threonine kinase 1; CKD4/6 = cyclin-dependent kinase 4 and 6; CR = complete response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IM = intramuscular; LHRH = luteinizing hormone–releasing hormone; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PIK3CA = catalytic α-subunit of phosphatidylinositol3kinase; PR = partial response; PTEN = Phosphatase

and tensin homolog; RECISTv1.1 = Response evaluation criteria for solid tumors version 1.1; WHO = World Health Organisation.

At the data cut for the primary analysis of PFS (15 August 2022), investigator-assessed PFS was significantly improved with capivasertib-fulvestrant compared with placebo-fulvestrant in the overall population and in the PIK3CA/AKT1/PTEN-altered population, which represents the licensed indication. Results are detailed in Table 2.2, along with results of exploratory subgroup analyses in those previously treated with a CDK4/6 inhibitor, who represents the proposed positioning, which suggest a PFS benefit with capivasertib. At this data cut, interim overall survival (OS) analyses in the PIK3CA/AKT1/PTEN-altered population were descriptive but at the 15 April 2024 data cut they were inferential with no significant difference and hazard ratio (HR) of 0.88 (95% confidence interval [CI]: 0.65 to 1.19). There were similar results in final analysis of OS, 16 June 2025.[1-3, 7, 8]

Table 2.2 Results of CAPItello-291 study in PIK3CA/AKT1/PTEN-altered population.[1-3, 7, 8]

	PIK3CA/AKT1/PTEN-altered		**PIK3CA/AKT1/PTEN-altered with prior CDK4/6 inhibitor**	
	Capivasertib-fulvestrant	**Placebo-fulvestrant**	**Capivasertib-fulvestrant**	**Placebo-fulvestrant**
	N=155	**N=134**	**N=114**	**N=94**
Progression-free survival, investigator-assessed on RECISTv1.1, data cut 15 August 2022				
PFS events, n	121	115	93	85
Median PFS, months	7.3	3.1	5.5	2.0
Hazard ratio (95% CI)	0.50 (0.38 to 0.65), p<0.001		0.49 (0.36 to 0.66)	
KM estimated PFS at 1 year	28%	16%	-	-
Overall survival, data cut 16 June 2025				
Deaths, n	109	98	83	74
Median OS, months	28.5	30.4	28.1	21.2
Hazard ratio (95% CI)	0.83 (0.63 to 1.10), p=0.201		0.78 (0.57 to 1.07)	
KM estimated OS at 2.5 years	49%	51%	-	-
Objective response rate, investigator-assessed on RECISTv1.1, data cut 15 August 2022				
Objective response, % (n/N)	29% (38/132)	9.7% (12/124)	-	-
Complete response, % (n/N)	1.9% (3/132)	0	-	-
Odds ratio (95% CI)	3.93 (1.93 to 8.04)		-	-
Median DOR, months	9.4	8.6	-	-

Abbreviations: CKD4/6 = cyclin-dependent kinase 4 and 6; CI = confidence interval; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; RECISTv1.1 = Response evaluation criteria for solid tumors version 1.1.

2.2. Evidence to support the positioning proposed by the submitting company

Evidence to support the proposed positioning is from the subgroup of the PIK3CA/AKT1/PTEN-altered population previously treated with a CDK4/6 inhibitor detailed in Table 2.2.

2.3. Health-related quality of life outcomes

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific module (EORTC QLQ-BR23) and the EuroQol EQ-5D-5L questionnaire. There were generally no clinically relevant differences in quality of life between the treatment groups.[2]

2.4. Supportive studies

A double-blind phase II study (FAKTION) recruited post-menopausal patients from UK sites with oestrogen receptor (ER)-positive, HER2-negative metastatic or locally advanced breast cancer. Their cancers had relapsed on or within 12 months of adjuvant aromatase inhibitor therapy or had progressed on an aromatase inhibitor in the metastatic setting (although this did not need to be the most recent therapy). All patients received fulvestrant 500 mg IM injections every 28 days, with an additional dose on Day 15 and were randomised to placebo (n=71) or the licensed dose of capivasertib (n=69). Treatment continued until disease progression of unacceptable toxicity. The primary outcome, investigator-assessed PFS on RECIST, significantly improved with capivasertib-fulvestrant versus placebo-fulvestrant, with a HR of 0.58 (95% confidence interval [CI]: 0.39 to 0.84).[2, 9] Updated analyses at the 25 November 2021 data cut, indicated an OS HR of 0.66 (95% CI: 0.45 to 0.97). At this data cut, in the subgroup of 63 patients with PIK3CA/AKT1/PTEN-altered tumours, PFS HR was 0.36 (95% CI: 0.20 to 0.65) and OS HR was 0.44 (95% CI: 0.24 to 0.81).[10]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing capivasertib-fulvestrant with everolimus-exemestane, the submitting company presented a Bayesian network analysis, as detailed in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian Network meta-analysis (with time varying hazards).
Population	Adults with hormone receptor-positive metastatic or locally advanced breast cancer that was human epidermal growth factor receptor 2-negative, unknown or positive.
Comparators	Capivasertib-fulvestrant versus fulvestrant; everolimus-exemestane versus fulvestrant (Capivasertib-fulvestrant versus exemestane-everolimus; not used in economics).
Studies included	**PFS**: CAPItello-291,[3] FAKTION,[9, 10] BOLERO-2,[11] BOLERO-5,[12] EFECT,[13] SOFEA,[14] CONFIRM,[15] FRIEND,[16] NCT01300351 (Zhang).[17] **OS**: CAPItello-291,[3] FAKTION,[9, 10] BOLERO-2,[11] SOFEA,[14] CONFIRM.[15]
Outcomes	PFS and OS
Results	Two sets of results were presented. One compared capivasertib-fulvestrant with a variety of medicines, including exemestane-everolimus; there appeared to be no evidence of difference between these for PFS and OS (except for PFS from months 0 to 3 in the fixed effect model only). These results were not included in the economic analyses, instead, the analyses were informed by fixed effect comparisons in which fulvestrant was used as the reference treatment for comparisons with capivasertib-fulvestrant and with exemestane-everolimus. These comparisons with fulvestrant suggest a larger benefit in PFS and OS with capivasertib-fulvestrant than everolimus-exemestane, during period one (0 to 3 months for PFS and 0 to 6 months for OS), but similar effects in period two (after 3 for PFS and 6 months for OS).

Abbreviations: CrI = credible interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

The addition of capivasertib to fulvestrant increased toxicity. In data from first data cut (15 August 2022) of CAPItello-291 in the overall population, capivasertib compared with placebo was associated with higher rates of adverse events: 97% (343/355) versus 82% (288/350); adverse events that were related to capivasertib or placebo (86% versus 47%); at least grade three severity

(43% versus 16%); serious (16% versus 8.0%,), fatal (1.1% versus 0.3%) and associated with discontinuation of capivasertib or placebo (13% versus 2.3%).[2, 18]

In the overall population at 15 August 2022 and in the PIK3CA/AKT1/PTEN-altered population at 15 April 2024 data cut, the capivasertib group compared with placebo had higher rates of gastrointestinal adverse events, including diarrhoea (72% versus 20%), nausea (35% versus 15%), vomiting (21% versus 4.9%) and stomatitis (20% versus 5.7%); hyperglycaemia (16% versus 3.7%); urinary tract infection (10% versus 6.6%) and QT interval prolongation (3.1% versus 0). Rash was reported at a higher rate with capivasertib in the overall population at the first data cut (38% versus 7.1%) and this occurred with greater severity (grade ≥3, 12% versus 0.3%). In the PIK3CA/AKT1/PTEN-altered population at 15 April 2024 data cut, capivasertib compared with placebo had higher rates of rash and maculo-papular rash . Rash was managed with systemic corticosteroids, which can induce hyperglycaemia, in about third of patients.[2, 18]

The European regulator noted that the lack of safety data in patients with Type 1 and 2 diabetes requiring insulin treatment or with HbA_{1c} ≥8.0% will be addressed by other phase III studies that permit their inclusion (such as CAPItana, CAPItrue and CAPIcorn) and by a non-comparative post-authorisation study that will specifically recruit these patients.[2]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In a phase III study, addition of capivasertib to fulvestrant significantly increased median PFS by about 4.2 months in patients with PIK3CA/AKT1/PTEN-altered tumours and by about 3.5 months in the subgroup previously treated with a CDK4/6 inhibitor, which represents the proposed positioning. The results of this study were considered clinically relevant by a regulator.[2, 3]
- Capivasertib is the first AKT inhibitor to be licensed for the treatment of advanced breast cancer.[1]

4.2. Key uncertainties

- The evidence to support the licensed indication is from a pre-specified, adequately powered subgroup (n=289), the PIK3CA/AKT1/PTEN-altered population.[2, 3] However, the proposed positioning is supported by data from an exploratory subgroup of these patients who had previously been treated with a CDK4/6 inhibitor (n=208).
- There was no direct comparative evidence for capivasertib-fulvestrant versus capecitabine, which was identified by clinical experts and CMOP data as a common treatment option in Scotland for patients with HR-positive HER2-negative advanced breast cancer that has progressed after first-line CDK4/6 inhibitor in combination with an aromatase inhibitor.
- In the resubmission it is assumed that the efficacy of capecitabine is the same as that of everolimus-exemestane based on assumptions in the manufacturer's economic model for National Institute of Health and Clinical Excellence (NICE) technology appraisal 421. However, the NICE committee concluded that robust comparisons between everolimus-

exemestane and chemotherapy (including capecitabine) were not possible based on the available evidence.[19] The BOLERO-6 study, which supports the licence for everolimus, was designed to meet regulatory requirements for estimates of treatment benefit but was not powered for inferential comparisons. It found that in post-menopausal patients with ER-positive, HER2-negative advanced breast cancer that had progressed after an aromatase inhibitor, everolimus-exemestane and capecitabine were associated with median PFS of 8.4 and 9.6 months, respectively, with a HR of 1.26 (90% CI: 0.96 to 1.66) favouring capecitabine. The HR for OS was 1.33 (90% CI: 0.99 to 1.79) with median OS of 23.1 and 25.6 months for the respective treatments.[20] The NMA was not updated to include this study and no direct or indirect comparative data for capivasertib-fulvestrant versus capecitabine have been presented.

- The indirect comparison of capivasertib-fulvestrant with everolimus-exemestane has some limitations. The cut-offs for varying hazards (3 months for PFS and 6 months for OS) were based on visual inspection of hazard profiles of the Kaplan-Meier curves. The economic analysis was informed by results from the fixed effect model, which (in contrast to the random effects model) does not account for heterogeneity across studies. Although point estimates of HR from the models were similar, credible intervals were wider in the random effects model, including the possibility of no difference between capivasertib-fulvestrant and everolimus-exemestane for OS or PFS. This was not used in the economic analysis, which was informed by HR from the NMA for fulvestrant versus capivasertib-fulvestrant and versus everolimus-exemestane. The indirect comparison is limited by heterogeneity across the studies, including changing treatment pathways over time, previous treatment and line of therapy, HER2 status and only the capivasertib studies provided data from the PIK3CA/AKT1/PTEN-altered population, which represents the indication. There was variation in the methods for assessing PFS, including assessment schedules, and in maturity of OS data. The indirect comparison did not assess quality of life or safety outcomes. Due to these limitations, the results are uncertain.
- The incidence of hyperglycaemia in CAPItello-291 may be lower than that observed in practice as it excluded patients who had $HbA_{1C} \geq 8.0\%$ (63.9 mmol/mol) or had diabetes mellitus type 1 or type 2 requiring insulin treatment and the protocol specified intensive management of hyperglycaemia with patients given education on lifestyle changes (such as diabetic diet) and home glucose monitoring. The European regulator noted that additional data on the safety (and efficacy) in patients with diabetes are needed to give guidance to prescribers and this should be provided by ongoing studies.[2]

4.3. Clinical expert input

Clinical experts consulted by SMC consider that capivasertib is a therapeutic advance in the treatment of HR-positive HER2-negative advanced breast cancer with PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen due to its efficacy compared with a current standard of care and targeted mechanism of action. They advise that it is likely to be used in accordance with its licensed indication but note issues in identifying patients with PIK3CA/AKT1/PTEN-alterations due to availability of testing in NHS Scotland.

4.4. Service implications

Genomic testing for PIK3CA/AKT1/PTEN-alterations is required to identify patients eligible for treatment with capivasertib. This testing is not currently routinely conducted in NHS Scotland.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of capivasertib, as an orphan equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced HR-positive, HER2-negative breast cancer is an incurable, life-limiting condition that is associated with substantial symptoms that may limit the patient's ability to care for themselves or dependents and to work or socialise. It affects a large group of patients at a time in their life when they have a pivotal family role, caring for children and elderly relatives while working. The patient's family may have to support them and help them attend healthcare appointments. Overall, the disease has an immense physical, practical and psychological impact, with patients and their family feeling afraid and anxious.

- After recurrence or progression on first-line hormonal therapy, treatment is individualised but options have limited efficacy and some, especially some chemotherapy options, have substantial toxicity and disruptive life-changing administration schedules. None target PIK3CA/AKT1/PTEN mutations. There is an unmet need for more effective therapies, including targeted treatments, with acceptable tolerability and administration schedules.

- Capivasertib targets AKT, which is activated in cancers with PIK3CA/AKT1/PTEN mutations and the addition of it to fulvestrant significantly improves progression-free survival compared with fulvestrant alone. It is given orally (with a once-monthly intramuscular injection of fulvestrant), which is less disruptive than intravenous options. This gives the patient an extended period during which they are well and able to lead a more normal life and be less reliant on their family for support. It may allow the patient to resume their family, work and societal roles and give them more time to enjoy with family. It may allow them to plan and give hope of surviving until more treatments become available. Accessing capivasertib may provide reassurance that optimal treatment is being given, which targets the specific mutation within the cancer.

- Clinical experts advised that capivasertib would be used for patients previously treated with a CDK4/6 inhibitor and in accordance with its licence which specifies the mutation. They note that additional resource may be required for genomic testing.

- Capivasertib is orally administered, therefore, patients only need to attend healthcare appointments to receive the fulvestrant part of the regimen, which is given every 28 days. Patients advise that they are happy to risk the side effects associated with capivasertib to access the benefits in progression-free survival. Clinicians noted that side effects are similar to those with other cancer medicines and are manageable.

Additional Patient and Carer Involvement

We received patient group submissions from: Breast Cancer Now, Make 2nds Count and METUP UK. All three organisations are registered charities. Breast Cancer Now has received 0.52% pharmaceutical company funding in the past two years, including from the submitting company. Make 2nds Count has received 17% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has not received any pharmaceutical company funding in the past two years. Representatives from all three patient groups participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime horizon (20 years) with a starting age of 59 years.
Population	Patients included in the economic model matched the indicated licence.
Comparators	Fulvestrant monotherapy and everolimus-exemestane were chosen as relevant comparators for this submission. The submitting company included chemotherapy (capecitabine) as a comparator within scenario analysis.
Model description	A partitioned survival model was used, comprising of three health states: progression-free (PF), progressed disease (PD), and death. The model was implemented with a monthly cycle length and a half-cycle correction applied. Health state occupancy was determined using PFS and OS curves. Time-to-treatment discontinuation (TTD) was modelled separately from PFS, by applying a ratio between TTD and PFS. Subsequent treatments following progression were included in the model for costs only and were applied based estimated proportions of subsequent treatments from Scottish clinical experts consulted by the submitting company.
Clinical data	The primary clinical data source was the CAPItello-291 study[2, 32, 32, 3], which provided patient-level data for the fulvestrant monotherapy arm, used as the reference for extrapolating PFS and OS in the economic model. Patient characteristics were also derived from this study. Resource use assumptions were based on data from NICE CG81 and other relevant appraisals and the opinion of Scottish clinicians consulted by the submitting company.[21] In the absence of direct comparative data against everolimus-exemestane, an NMA was conducted to estimate relative treatment effects. The NMA informed time varying hazard ratios for both PFS (0-3 months, and after 3 months) and OS (0-6 months, and after 6 months). Efficacy of capecitabine was assumed equal with everolimus-exemestane, matched to the assumptions made in other HTA submissions by the submitting company.
Extrapolation	Extrapolation of PFS and OS was based on the fulvestrant monotherapy arm from the CAPItello-291 study. Parametric functions were fitted to the Kaplan-Meier data for this arm and extrapolated over a lifetime horizon. The log-logistic curve was selected for both PFS and OS. Relative treatment effects for the capivasertib-fulvestrant and everolimus-exemestane

	arms were applied via time varying hazard ratios obtained from the NMA, see Table 2.3 for details. Background mortality was applied using general population life tables. Adjustment for treatment waning was applied in a scenario analysis at five years.
Quality of life	Health-related quality of life was estimated using EQ-5D-5L data collected in the CAPItello-291 study and mapped to EQ-5D-3L using Hernández Alava et al., (2017) algorithm.[22] Utility values were assigned to the PF and PD health states and applied equally across treatments. Utilities associated with grade 3 or higher adverse events (AEs) were sourced from various studies, following the same approach as a previous HTA submission for abemaciclib with fulvestrant (TA725).[23] Additional AE disutilities were sourced for chemotherapy, specifically for fatigue, Palmar-Plantar Erythrodysesthesia (PPE) syndrome and neutropenia. These AE disutilities were applied as one-off decrements in the model.
Costs and resource use	Costs in the model included medicine acquisition, administration, subsequent treatments following progression, disease monitoring, disease managements, resource use, end of life costs and testing costs.
PAS/contract price	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount of was offered on the list price. PAS discounts and contract prices are in place for fulvestrant, everolimus and capecitabine, and these were included in the results used for decision-making.

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.3.

Table 6.3: Sensitivity and Scenario Analysis Results

	Parameter	Base case	Scenario
	Base case		
1	PFS distribution	Log-logistic	log-normal
2			Generalised gamma
3	OS distribution	Log-logistic	Weibull
4			Log-normal
5	NMA Cut points for PFS	0-3 months, >3 months	0-2 months and >2months
6	Relative treatment effects (HR)	Time varying NMA HR point estimate was used (value AiC)	Using lower bound 95% credible interval HR for everolimus-exemestane and capecitabine OS before 6 months (value AiC)
7		Time varying NMA outputs	Assuming equal OS efficacy of fulvestrant monotherapy and everolimus-exemestane and capecitabine
8		Time varying NMA outputs	Capivasertib and everolimus-exemestane and chemotherapy 95% lower bound HR credible intervals for

			OS and PFS
9	Capecitabine HRs	100% of everolimus-exemestane	90% of everolimus-exemestane
10	HR for everolimus-exemestane and capecitabine vs capivasertib	Point estimate HR values	Lower CI values for everolimus-exemestane and capecitabine, point estimate values for capivasertib
11	NMA model choice	Fixed effects model	Random effects model
12	Treatment waning	No treatment waning	Treatment waning at 5 years
13	Time-to-treatment discontinuation	HR applied to PFS for TTD (all comparators): (value AiC)	HR applied to PFS for TTD (all comparators: (value AiC)
14	Utilities	EQ-5D data (value AiC)	Using PD health state utility value from SMC2481 (0.69)
16	Time horizon	20 years (lifetime)	10 years

Abbreviations: AiC; academic in confidence; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

6.4. Key strengths

- Fulvestrant monotherapy, everolimus-exemestane and chemotherapy (capecitabine) were included as comparators, which reflects Scottish clinical practice according to SMC experts.
- The submitting company employed a de novo partitioned survival model, which was an appropriate model structure.
- Health state utilities were derived using EQ-5D data collected in the pivotal CAPItello-291 study.
- The model incorporated AE incidence rates based on study population.
- A treatment waning effect was included.

6.5. Key uncertainties

- The CAPItello-291 study provided evidence against fulvestrant monotherapy; there is no direct comparison with everolimus-exemestane or chemotherapy. As a result, relative treatment effects rely on an NMA, introducing uncertainty. The NMA is limited by immature OS data, wide confidence intervals, and potential heterogeneity across included studies. The submitting company used a fixed effects model on the basis of goodness-of-fit statistics, but a random effects model may have been more appropriate to show more clearly the extent of uncertainty associated with this approach.
- The NMA was not updated to include the BOLERO-6 study which might have allowed chemotherapy (capecitabine) to be included fully in the revised analysis rather than having an assumption of equivalent efficacy to everolimus-exemestane. The submitting company has argued that the BOLERO-6 study has too high a risk of bias to include, but it was noted that the economic model is sensitive to the assumption of equivalent efficacy between everolimus-exemestane and capecitabine (see Scenarios 6 to 10, Table 6.3), and that this assumption may not hold true in clinical practice.
- Extrapolation of OS remains an area of uncertainty in the economic model. The majority of the QALY gain for all treatments was being accrued in the progressed disease state and OS in this state was largely extrapolated beyond the latest available follow-up data, so the assumptions influencing the QALY gain (OS, continued treatment effect and health state

utilities for the progressed disease state) were key parameters which could have been more extensively tested in scenario analysis.

7. Conclusion

The Committee considered the benefits of capivasertib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as capivasertib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted capivasertib for restricted use in NHSScotland.

8. Guidelines and Protocols

In May 2026, the European Society of Medical Oncology (ESMO) published 'Metastatic breast cancer: ESMO Clinical Practice Guideline for the diagnosis, treatment and follow-up.'[24]

In February 2025, the National Institute for Health and Care Excellence (NICE) updated clinical guideline 81 (CG81): 'Advanced breast cancer: diagnosis and treatment.'[25]

9. Additional Information

9.1. Product availability date

17 July 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Capivasertib Fulvestrant	400 mg orally twice daily for first 4 days of every week 500 mg IM on Day 1, 15 and 29 then every 28 days	6,372 (6,895 – first cycle)

Costs from BNF online on 20 May 2026. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 4 patients eligible for treatment with capivasertib-fulvestrant in year 1 and 30 in year 3. Approximately 53 new patients meeting the licensed indication for capivasertib-fulvestrant are diagnosed each year. The estimated uptake rate was 13% in year 1 and 70% in year 3. This resulted in 1 patient estimated to receive treatment in year 1 rising to 21 patients in year 3.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 July 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.