SMC2823

capivasertib film-coated tablet (Truqap®)

AstraZeneca UK

05 September 2025

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 full submission assessed under the end of life and orphan equivalent medicine process

capivasertib (Truqap®) is not recommended for 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.

In a double-blind, phase III study, addition of capivasertib to fulvestrant significantly improved progression-free survival in adults with locally advanced or metastatic HR-positive HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations who had recurrence or progression on or after an aromatase inhibitor-based regimen.

The company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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.[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. For those with an initial good 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 November 2022, that it is not accepted 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]

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, 3]

Table 2.1. Overview of relevant studies.[2, 3]

Criteria	CAPItello-291
Study design	Double-blind, international, phase III study
Eligible patients	Pre-, peri- or post-menopausal women and men (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 aromatase inhibitor therapy. 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 thereafter. 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). Prior CDK4/6 inhibitor ≥51%.
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').
Secondary outcomes	OS, defined as the time from randomisation to death from any cause.
Statistical analysis	The co-primary outcomes and OS were controlled for multiplicity.

Abbreviations: CKD4/6 = cyclin-dependent kinase 4 and 6; 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; OS = overall survival; PFS = progression-free survival; RECISTv1.1 = Response evaluation criteria for solid tumors version 1.1; WHO = World Health Organisation.

At the data cut-off 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 the PIK3CA/AKT1/PTEN-altered population, which represents the licensed indication. The 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 cut-off, interim overall survival (OS) analyses in the PIK3CA/AKT1/PTEN-altered population were descriptive but at the 15 April 2024 cut-off they were inferential with no significant difference. The study is ongoing, and the final assessment of OS is awaited.[1-3, 6]

Table 2.2 Results of CAPItello-291 study in PIK3CA/AKT1/PTEN-altered population.[1-3, 6, 7]

	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-off 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-off 15 August 2022				
Deaths, n	41	46	33	39
Hazard ratio (95% CI)	0.69 (0.45 to 1.05)		0.63 (0.40 to 1.00)	
KM estimated OS at 18 months	73%	63%	-	-
Overall survival, data cut-off 15 April 2024				
Deaths, n	*	*	*	*
Median OS, months	*	*	*	*
Hazard ratio (95% CI)	0.88 (0.65 to 1.19)		*	
KM estimated OS at 2 years	*	*	-	-
Objective response rate, investigator-assessed on RECISTv1.1, data cut-off 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; * results considered confidential by the company

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

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 capivasertib 400 mg orally twice daily on a weekly schedule that included 3 days off treatment (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, 8] Updated analyses at the 25 November 2021 cut-off, indicated an OS HR of 0.66 (95% CI: 0.45 to 0.97). At this cut-off, 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).[9]

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

The company provided a Bayesian Network meta-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,[8, 9] BOLERO-2,[10] BOLERO-5,[11] EFECT,[12] SOFEA,[13] CONFIRM,[14] FRIEND,[15] NCT01300351 (Zhang).[16] **OS**: CAPItello-291,[3] FAKTION,[8, 9] BOLERO-2,[10] SOFEA,[13] CONFIRM.[14]
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 significant differences between these in 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 analysis, which was informed by the results from the fixed effect comparisons of fulvestrant (as a reference) versus capivasertib-fulvestrant and versus 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: PFS = progression-free survival; OS = overall survival

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

3. Summary of Safety Evidence

Evidence from the CAPItello-291 study supports the relative safety for capivasertib-fulvestrant compared with fulvestrant monotherapy, which is considered a relevant comparator in this submission.

The addition of capivasertib to fulvestrant increased toxicity. Data from the first cut-off (15 August 2022) of CAPItello-291 in the overall population are similar to the PIK3CA/AKT1/PTEN-altered population at the 15 April 2024 cut-off, which are commercial in confidence. At the first cut-off, 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, 7]

In the overall population at the 15 August 2022 cut-off, the capivasertib group compared with placebo had higher rates of gastrointestinal adverse events, including diarrhoea (72% versus 20%), nausea (35% versus 15%), vomiting (20% 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-off (38% versus 7.1%) and this occurred with greater severity (grade ≥3, 12% versus 0.3%). Rash was managed with systemic corticosteroids, which can induce hyperglycaemia, in about third of patients.[2 7]

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, CAPIture 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 the European regulator.[2, 3]
- Capivasertib is the first AKT inhibitor to be licensed for the treatment of advanced breast cancer. Clinical experts consulted by SMC note that capivasertib fulfils an unmet need for more therapeutic options, especially targeted treatments.

4.2. Key uncertainties

- At the most recent interim analysis (April 2024) of CAPItello-291, OS data are immature, and there was no significant difference between the treatment groups.[1] The final analysis of OS is awaited.
- The evidence to support the licensed indication is from a pre-specified, adequately powered subgroup (n=289), the PIK3CA/AKT1/PTEN-altered population. 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).[2, 3]

- For patients with an initial good response to first-line therapy (CDK4/6 inhibitor plus aromatase inhibitor), second-line treatment options include single-agent chemotherapy (such as capecitabine or paclitaxel) or further endocrine-based therapy (such as fulvestrant monotherapy or exemestane-everolimus).[4] Single-agent chemotherapy was not considered a comparator in the submission and no direct or indirect comparison was made, despite clinical experts consulted by SMC highlighting that capecitabine is one of the treatments most likely to be displaced by the availability of capivasertib.
- Capivasertib, which is licensed for use with the endocrine therapy, fulvestrant, was noted to be an option for patients who choose further endocrine-based therapy. CAPItello-291 provided direct evidence versus fulvestrant monotherapy. However, as there was no direct comparison versus everolimus-exemestane, an indirect comparison informed the economic analysis.
- 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 subjective. 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 exemestane-everolimus for OS or PFS. This was not used in the economic analysis, which was informed by HR from the network meta-analysis (NMA) for fulvestrant versus capivasertib-fulvestrant and versus exemestane-everolimus. The indirect comparison is limited by heterogeneity across the studies, including the 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]
- Scottish clinical management pathways note that patients with rapid progression on first-line therapy should be considered for chemotherapy second-line.[4] CAPItello-291 excluded patients with a disease burden that made them ineligible for endocrine therapy (such as those with symptomatic visceral disease that was potentially life-threatening in the short-term). As capivasertib-fulvestrant has not been studied in patients who have rapidly progressing disease, it is unlikely to be an alternative for chemotherapy in these patients.

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

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 when they are well and able to lead a more normal life, being 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 0.5% pharmaceutical company funding in the past two years, with none 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 received 23% pharmaceutical company funding in the past two years, including from the submitting company. 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

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 in the economic analysis match the companies proposed positioning, which was 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 and progressed following CDK4/6 inhibitor plus aromatase inhibitor therapy.
Comparators	Fulvestrant monotherapy and everolimus-exemestane were the included comparators for this submission.
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, based on observed ratios from study data. Subsequent treatments following progression were included in the model for costs only and were applied based on market research data.
Clinical data	The primary clinical data source was the CAPItello-291 study[2, 3], which provided patient-level data for the fulvestrant monotherapy arm, used as the reference for extrapolating PFS and OS in the economic model. Population properties and resource use assumptions were also derived from this study. 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).
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 rations obtained from the NMA (see Table 2.3 for further details). Background mortality was applied using general population life tables. No adjustment for treatment waning was applied.
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.[17] 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 were sourced from various studies, following the same approach as a previous HTA submission for abemaciclib with fulvestrant (TA725).[18] These adverse events 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 and end of life costs. A cost for genetic testing was included as this was not routine practice in Scotland.
PAS	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 was offered on the list price. A PAS discount is in place for fulvestrant and everolimus, and this was included in the results used for decision-making by using estimates of the comparator PAS price. SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

6.2. Results

The base case economic results suggested that capivasertib-fulvestrant was associated with higher costs, but also better health outcomes when compared to everolimus-exemestane and fulvestrant monotherapy. Due to the presences of confidential PAS discounts on capivasertib, fulvestrant and everolimus SMC is unable to present decision-making economic results.

*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 6.2.

Table 6.2: Sensitivity and Scenario Analysis Results

				ICER (£/QALY)	
	Parameter	**Base case**	**Scenario**	**Vs. everolimus-exemestane**	**Vs. fulvestrant monotherapy**
	Base case			***CiC***	***CiC***
1	Time horizon	20 years (lifetime)	10 years	***CiC***	***CiC***
2	PFS distribution:	Log-logistic	log-normal	***CiC***	***CiC***
3			Generalised gamma	***CiC***	***CiC***
4	OS distribution	Log-logistic	gamma	***CiC***	***CiC***
5			Weibull	***CiC***	***CiC***
6	NMA Cut points for PFS	0-3 months, >3 months	0-2 months and >2months	***CiC***	***CiC***
7	Relative treatment effects (HR)	Mean outputs from NMA	Lower confidence interval HR for	***CiC***	***CiC***

			everolimus-exemestane OS before 6 months		
8			Assuming equal OS efficacy of fulvestrant monotherapy and everolimus-exemestane	***CiC***	***CiC***
9	NMA structure	Fixed effects	Random effects	***CiC***	***CiC***
10	Time-to-treatment discontinuation	Average ratio of PFS to TTD from CAPItello-291 for capivasertib-fulvestrant applied to PFS (all comparators)	Lower bound of PFS to TTD from CAPItello-291 for capivasertib-fulvestrant applied to PFS (all comparators)	***CiC***	***CiC***
11	Progressed disease utility estimate	Estimated from EQ-5D data collected in CAPItello-291	Matched to SMC2481	***CiC***	***CiC***

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PFS, progression-free survival; OS, overall survival; PD, progressed disease; HR, hazard ratio; NMA, network meta-analysis; TTD, time to treatment discontinuation

6.4. Key strengths

- The company employed a de novo partitioned survival model, which is an appropriate model structure.
- Health state utilities were derived using EQ-5D data collected in the pivotal CAPItello-291 study.
- The model incorporated adverse event incidence rates based on study population.

6.5. Key uncertainties

- While the CAPItello-291 provides evidence against fulvestrant monotherapy, there is no direct comparison with everolimus-exemestane. As a result, relative treatment effects rely on an NMA, introducing uncertainty. The NMA is limited by immature overall survival data, wide confidence intervals, and potential heterogeneity across included studies. While, the company used a fixed effects model, a random effects model may have been more appropriate. The random effects model led to only a modest change in the estimated cost-effectiveness (see Scenario 9, Table 6.3), however, the wider confidence intervals may have better captured the uncertainty. A time-varying approach was used to address proportional hazards, but the selection of time cut points was based on visual inspection, and there was minimal exploration of alternative cut points.
- The company's approach applies time-varying hazard ratios, which account for the diminishing treatment effects over the study period. While this captures some waning of effect, there remains some residual uncertainty around the long-term maintenance of treatment benefit beyond the observed data.
- The extrapolation of overall survival was a key uncertainty and one which could impact the results. Although a systematic approach was taken in selecting the base case model, other

survival distributions, which produce lower long-term survival estimates, do impact the cost-effectiveness results (Scenarios 4 and 5).

- The bulk of the QALY gains for all treatments is accrued in the PD state, and since survival in this state is largely extrapolated and subject to assumptions about sustained treatment effect, this compounds the uncertainty surrounding the long-term benefit estimates.
- An area of uncertainty was the exclusion of chemotherapy as a comparator. The company maintained that chemotherapy was not relevant, but did provide a scenario that compared capivasertib-fulvestrant against chemotherapy, using capecitabine as a proxy for all chemotherapies. In this scenario, chemotherapy is assumed to have equal efficacy to everolimus-exemestane. This gave an approximate estimate of the potential impact, but uncertainty remained around how well it reflects the full range of relevant treatment options and their comparatives effectiveness in clinical practice.
- The cost of everolimus and fulvestrant in NHS practice is lower than the price used in the economic model due to the existence of a national framework agreement for this medicine. Using the national framework contract price has a moderate upward impact on the cost-effectiveness results.

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 was unable to accept capivasertib for use in NHSScotland.

8. Guidelines and Protocols

In 2021, the European Society of Medical Oncology (ESMO) published ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer.[5]

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 20.5.25. 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

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

*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 11 July 2025**.**

**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 is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme 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. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards 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.