Indication	Capivasertib with fulvestrant for hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN genomic alterations following recurrence or progression on or after treatment with a CDK4/6 inhibitor and an aromatase inhibitor. NB: Patients may switch from alpelisib plus fulvestrant if treatment has had to be stopped within 6 months of its start solely as a consequence of excessive toxicity and in the clear absence of disease progression. NB the patient must have not received any prior treatment with fulvestrant for any indication, unless this patient has either received capivasertib plus fulvestrant via the company early access programme and all other conditions on this form are complied with or this patient is switching from treatment with alpelisib plus fulvestrant due to toxicity.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until disease progression, unacceptable toxicity or withdrawal of patient consent.

Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.
	• If the patient is female they should either be post-menopausal, or if pre- or peri-menopausal, should have undergone ovarian ablation or suppression with LHRH agonist treatment. If the patient is male, consideration has been given to administration of LHRH agonist therapy.
	• **Fasting glucose** (FG) and HbA1c should be undertaken prior to start of treatment and if abnormal, discuss with consultant and consider specialist diabetic advise.
	• FG baseline and day 15 of cycle 1 and at every cycle thereafter.
	• HbA1c baseline and every 3rd cycle thereafter.
	• Monitor FBC, U&Es, and LFTs at baseline and at each cycle thereafter.
	• **Haematological parameters:** NB: Platelets should be >/=50 for intramuscular injection with fulvestrant.
	  ○ If PLT >/=100 and neuts >/=1 proceed with treatment.
	  ○ If PLT 50-99 and neuts >/=1 discuss with consultant.
	  ○ If PLT <50 and neuts <1 delay both drugs for 1 week.
	• **Hepatic impairment:**
	• **Capivasertib:** No dose adjustment required in mild impairment (bilirubin </=ULN and AST > ULN or bilirubin >1.0x - 1.5 x ULN). Limited data are available in moderate impairment (bilirubin >1.5x - 3.0 x ULN); use only if the benefit outweighs the risk with close monitoring for adverse effects. Not recommended in severe impairment (bilirubin >3.0x ULN) no data available.
	• **Fulvestrant:** No dose adjustment of fulvestrant is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B), although use fulvestrant with caution. No data for the use of fulvestrant in severe hepatic impairment.
	• **Renal impairment:**
	• **Capivasertib:** No dose adjustment required in mild, or moderate renal impairment (CrCl >/=30 mL/min). Not recommended in severe renal impairment CrCl <30ml/min, insufficient data are available, use with caution.
	• **Fulvestrant:** No dose adjustment of fulvestrant is required for patients with mild or moderate renal impairment (CrCl >/=30 mL/min). Insufficient data are available in patients with severe renal impairment to provide any dose adjustment recommendation, administer with caution.

- **Monitoring and Management of adverse reactions:**
- **Dose Modification for adverse reactions:**
- Dose interruption or reduction may be required for adverse reactions, see tables 1, 2, 3 and 4 below. The first dose reduction for adverse reactions is 320mg BD (2 x 160mg tablets), the second dose reduction is 200mg BD (1 x 200mg tablet) no further dose reductions are permitted. If a patient cannot tolerate 200mg BD, treatment should be discontinued. NB: See below for guidance on dose reductions with a concomitant CYP3A4 inhibitor.
  In patients who suffer a severe allergic reaction / toxicity which necessitates discontinuation of the drug causing the severe allergy / toxicity, use of capivasertib or fulvestrant can continue as monotherapy.
- **Hyperglycaemia:** Severe hyperglycaemia, associated with diabetic ketoacidosis, has been reported in patients treated with capivasertib. If a patient develops hyperglycaemia specialist diabetic advise should be obtained.
  - More frequent FG testing is required in patients with diabetes mellitus, in patients without prior history of diabetes mellitus and showing FG of > ULN 160 mg/dl (> ULN 8.9 mmol/L) during treatment or in those with intercurrent infections or other conditions which may require intensified glycaemia management to prevent worsening of impaired glucose metabolism and potential complications. Monitoring of HbA1C, ketones (preferably in blood) and other metabolic parameters (as indicated), in addition to FG, is recommended in these patients.
  - Based on the severity of hyperglycaemia, dose interruption, reduction or permanent discontinuation maybe be required (see table 1).
  - Patients with a diagnosis of diabetes mellitus must be closely monitored.
  - All patients should be advised on the signs and symptoms of hyperglycaemia and advised to contact the healthcare team immediately.
- **Diarrhoea:** Severe diarrhoea associated with dehydration and >/= Grade 3 hypokalaemia has been reported in patients treated with capivasertib. Dose interruption, reduction or discontinuation may be required, see table 3. Patients should be advised to start anti-diarrhoeal treatment at the first onset of diarrhoea, increase oral fluids and notify the SACT team.
- **Cutaneous adverse drug reactions:** Cutaneous adverse drug reactions, including erythema multiforme and dermatitis exfoliative generalised have been reported. Patients should be advised of the signs and symptoms of severe cutaneous reactions, dose interruption, reduction or discontinuation may be required, see table 2. Consultation with a dermatologist is recommended if symptoms occur.
- **Osteonecrosis of the jaw:** Patients with metastatic cancer receiving bisphosphonates or RANK-ligand inhibitors prior to or during treatment with capivasertib should be closely monitored for signs or symptoms of jaw osteonecrosis. Patients should be advised to promptly report any new or worsening oral symptoms including dental mobility, pain or swelling, non-healing of mouth sores or discharge during treatment with capivasertib. In patients who develop osteonecrosis of the jaw, standard medical management should be initiated.
  https://www.uksactboard.org/medication-related-osteonecrosis-of-the-jaw-guidance-for-the-oncology-multi-disciplinary-team
- **Common drug / food interactions (for comprehensive list refer to BNF/SPC):**
- **Capivasertib:**
- Co-administration with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) increases capivasertib concentration, which may increase the risk of toxicity. Co-administration with moderate CYP3A4 inhibitors (e.g. aprepitant, ciprofloxacin, cyclosporin) may increase capivasertib concentration. The dose of capivasertib should be reduced to 320 mg twice daily, 4 days on, 3 days off when concomitantly used with **strong** or **moderate** CYP3A4 inhibitors. Must not be taken with grapefruit or grapefruit juice.
- Concomitant use with strong (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) or moderate (e.g. modafinil, thioridazine) CYP3A4 inducers is not recommended.

	• Dose adjustment may be required for drugs that are primarily eliminated via CYP3A metabolism and have a narrow therapeutic window (e.g. carbamazepine, cyclosporin, fentanyl, simvastatin, tacrolimus). • Avoid co-administration with UGT2B7 inhibitors (e.g. probenecid, valproic acid) as there is potential for increase in capivasertib concentration, which may increase the risk of toxicity. • Avoid co-administration with UGT2B7 inducers (e.g. rifampicin) as there is potential for decrease in capivasertib concentration, which may affect efficacy. • Dose adjustment may be required for drugs that are primarily eliminated via CYP3A metabolism and have narrow therapeutic window (e.g., carbamazepine, cyclosporine, fentanyl, pimozide, simvastatin, tacrolimus). • Capivasertib interacts with hepatic transporters (OATP1B1, OATP1B3) and renal transporters (MATE1, MATE2K, OCT2). Depending on their therapeutic window, dose adjustment may be required for drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3 (e.g., simvastatin) if they are metabolised by CYP3A4 or MATE1, MATE2K, OCT2 (e.g. dofetilide, procainamide). • Sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with capivasertib, as clinical activity may be reduced. • **Missed dose:** If a dose of capivasertib is missed, it can be taken within 4 hours after the time it is usually taken. If more than 4 hours have passed, the dose should not be taken, the patient should take the next dose at its scheduled time. If the patient vomits, an additional dose should not be taken. • **Driving:** Caution when driving or using machines in case of fatigue during treatment. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	CDF list accessed online 16.04.2024, SPC accessed online 16.04.2025, BlueTeq form accessed online 16.04.2025. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2214131/suppl_file/nejmoa2214131_protocol.pdf https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00284-4/fulltext

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Recommended dose modification of capivasertib for hyperglycaemia

CTCAE Grade[a] and Fasting Glucose (FG)[b] values prior to capivasertib dose	Recommendation
Grade 1 > ULN-160 mg/dL or > ULN-8.9 mmol/L or HbA1C > 53mmol/mol	No dose adjustment required. Consider initiation or intensification of oral anti-diabetic treatment.
Grade 2 > 160-250 mg/dL or > 8.9-13.9 mmol/L	Initiate or intensify oral anti-diabetic treatment. Withhold until fasting glucose (FG) level decrease to ≤ 160 mg/dl (or ≤ 8.9 mmol/L). If recovery occurs in ≤28 days, resume at the same dose and maintain initiated or intensified anti-diabetic treatment. If improvement to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) is reached in more than 28 days restart at one lower dose level and maintain initiated or intensified anti-diabetic treatment.
Grade 3 > 250-500 mg/dL or > 13.9-27.8 mmol/L	Withhold until fasting glucose (FG) level decrease to ≤ 160 mg/dl (or ≤ 8.9 mmol/L) and consult a diabetologist. Initiate or intensify oral anti-diabetic treatment. Consider additional anti-diabetic medicinal products such as insulin, as clinically indicated. Consider intravenous hydration and provide appropriate clinical management as per local guidelines. If FG decreases to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) within 28 days, restart at one lower dose level and maintain initiated or intensified anti-diabetic treatment. If FG does not decrease to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) within 28 days following appropriate treatment permanently discontinue.
Grade 4 > 500 mg/dL or > 27.8 mmol/L)	Withhold and consult with a diabetologist. Initiate or intensify appropriate anti-diabetic treatment. Consider insulin, (dosing and duration as clinically indicated), intravenous hydration and provide appropriate clinical management as per local guidelines. If FG decreases to ≤ 500 mg/dl (or ≤ 27.8 mmol/l) within 24 hours, then follow the guidance in the table for the relevant grade. If FG is confirmed at > 500 mg/dl (or ≥ 27.8 mmol/l) after 24 hours, permanently discontinue treatment.

[a] Grading according to NCI CTCAE Version 4.03.
[b] Considerations should be also given to increases in HbA1C.

Table 2 Recommended dose modification for capivasertib for diarrhoea

CTCAE Grade[a]	Recommendation
Grade 1	No dose adjustment required. Initiate appropriate anti-diarrhoeal therapy, maximise supportive care and monitor as clinically indicated.
Grade 2	Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. Withhold dose for up to 28 days until recovery to ≤ Grade 1 and resume dosing at same dose or one lower dose level as clinically indicated. If Grade 2 diarrhoea is persistent or recurring, maintain appropriate medical therapy and restart at one lower dose level, as clinically indicated.
Grade 3	Withhold until recovery to ≤ Grade 1. Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. If recovery occurs in ≤ 28 days, resume at one lower dose level. If recovery to ≤ Grade 1 in > 28 days, permanently discontinue.
Grade 4	Permanently discontinue.

[a] Grade according to the NCI CTCAE Version 5.0.

Table 3 Recommended dose modification for capivasertib for Cutaneous Adverse Drug Reactions

CTCAE Grade[a]	Recommendation
Grade 1	No dose adjustment required. Initiate emollients and consider adding oral non -sedating antihistamine treatment as clinically indicated to manage symptoms.
Grade 2	Withhold until recovery to ≤ Grade 1. Initiate or intensify topical steroid treatment and consider non-sedating oral antihistamines. If recovery occurs in ≤ 28 days, resume at the same dose level. If persistent or recurrent: restart by one dose level.
Grade 3	Withhold until recovery to ≤ Grade 1. Initiate appropriate dermatological treatment with topical steroid of moderate/higher strength, non-sedating oral antihistamines and/or systemic steroids. If recovery occurs in ≤ 28 days, restart on one lower dose level. If the symptoms do not improve to ≤ Grade 1 within 28 days discontinue. In patients with reoccurrence of intolerable Grade 3 rash, permanently discontinue.
Grade 4	Permanently discontinue.

[a] Grade according to the NCI CTCAE Version 5.0.

Table 4 Dose modification and management for other toxicities (excluding hyperglycaemia, diarrhoea and, cutaneous adverse drug reactions)

CTCAE Grade[a]	Recommendation
Grade 1	No dose adjustment required, initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Withhold until symptoms improve to ≤ Grade 1.
Grade 3	Withhold until symptoms improve to ≤ Grade 1. If symptoms improve, restart at same dose or one lower dose level as clinically appropriate.
Grade 4	Permanently discontinue.

[a] Grade according to the NCI CTCAE Version 5.0.

Cycle 1: cycle length 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**FULVESTRANT**	**500mg**	intramuscular	Each 5ml (250mg) injection over 1-2 minutes	Administered as 2 x 250mg (5ml) injections, one in each buttock.
15	**FULVESTRANT**	**500mg**	intramuscular	Each 5ml (250mg) injection over 1-2 minutes	Administered as 2 x 250mg (5ml) injections, one in each buttock.
TTO	Drug	Dose	Route	Directions	
Day 1	**CAPIVASERTIB**	**400mg**	PO	BD for 4 consecutive days followed by a 3-day break (given as FOUR 7 day cycles): ***Take BD on days 1 to 4, days 8 to 11, days 15 to 18, days 22 to 25 only.*** To be taken approximately 12 hours apart, with the minimum of 8 hours between doses. Swallow whole with water, do not crush, chew or dissolve. Available as 160mg and 200mg tablets.	
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Dispense with cycle 1 and then only if required.	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense on cycle 1 and then only if required.	

Cycle 2 onwards: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**FULVESTRANT**	**500mg**	intramuscular	Each 5ml (250mg) injection over 1-2 minutes	Administered as 2 x 250mg (5ml) injections, one in each buttock.

TTO	Drug	Dose	Route	Directions
Day 1	**CAPIVASERTIB**	400mg	PO	BD for 4 consecutive days followed by a 3-day break (given as FOUR 7 day cycles): ***Take BD on days 1 to 4, days 8 to 11, days 15 to 18, days 22 to 25 only.*** To be taken approximately 12 hours apart, with the minimum of 8 hours between doses. Swallow whole with water, do not crush, chew or dissolve. Available as 160mg and 200mg tablets.
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Only supply if required.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Only supply if required.