CAPIVASERTIB (Truqap) FULVESTRANT

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (CAP1)

1. Capivasertib in combination with fulvestrant only for hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA or an AKT1 or a PTEN genomic alteration in patients previously treated with a CDK4/6 inhibitor and an aromatase inhibitor, and progressive disease after previous endocrine-based treatment, which is not amenable to curative treatment. Has had no prior treatment with fulvestrant for any indication. PS 0 or 1. (TA1063)

REGIMEN

Days 1 to 4, 8 to 11, 15 to 18 and 22 to 25	CAPIVASERTIB	400mg tablet oral twice daily
Day 1 (and day 15 cycle 1 only)	FULVESTRANT	500mg IM

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression

ADMINISTRATION

Available as 160mg and 200mg tablets
Swallow whole with or without food.
Fulvestrant each 500mg dose is administered as two consecutive 250mg (5 ml) injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).

ANTI-EMETICS

Low risk

CONCURRENT MEDICATION REQUIRED

Capivasertib	If the patient is female and pre- or peri-menopausal, or if the patient is male then they should also have undergone ovarian ablation or suppression with LHRH agonist treatment.. Cetirizine 10mg daily recommended to start prophylactically to prevent rash. Topical emollient prn for prevention / treatment of rash. Loperamide to be taken at onset of any diarrhoea and then prn.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before capivasertib administration
FBC, U&Es and LFTs baseline, every cycle
Platelets x 10^9/L >50
Fasting plasma glucose pre-initiation (>7.0 mmol/L consider initiation of diabetic medication), weeks 1, 2, 4, 6 and 8 weeks then every cycle (on day 3 or 4 of those weeks).
HbA1C baseline (>6.5% consider initiation of diabetic medication) then every 3 months
Blood creatinine

MAIN TOXICITES AND ADVERSE REACTIONS

Capivasertib	Anaemia Cutaneous reactions Diarrhoea, nausea, vomiting Hyperglycaemia Stomatitis UTI

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS (not exhaustive list check SPC/BNF/Stockleys)

Capivasertib	Strong CYP3A4 inhibitors increase capivasertib concentration, which may increase the risk of capivasertib toxicity. Reduce the dose of capivasertib. Moderate CYP3A4 inhibitors is predicted to increase capivasertib concentration. UGTB27 inhibitors has potential to increase capivasertib concentration. Bisphosphonates or RANK-ligand inhibitors monitor for signs or symptoms of jaw osteonecrosis.

DOSE MODIFICATIONS

Capivasertib

Recommended dose	400mg twice daily for 4 days, followed by 3 days off treatment
First dose reduction	320mg twice daily for 4 days, followed by 3 days off treatment
Second dose reduction	200mg twice daily for 4 days, followed by 3 days off treatment

Continue fulvestrant during capivasertib treatment breaks for toxicity

Non-haematological

Capivasertib

Cutaneous reactions

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

Diarrhoea

Grade 1	No capivasertib 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 capivasertib dose for up to 28 days until recovery to ≤grade 1 and resume capivasertib 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 capivasertib at one lower dose level, as clinically indicated.
Grade 3	Withhold capivasertib until recovery to ≤grade 1. Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. If recovery occurs in ≤28 days, resume capivasertib at one lower dose level. If recovery to ≤grade 1 in >28 days, permanently discontinue capivasertib.
Grade 4	Permanently discontinue capivasertib.

Hyperglycaemia

Grade 1 >ULN-160mg/dL or >ULN-8.9mmol/L or HbA1C >7%	No capivasertib dose adjustment required. Consider initiation or intensification of oral anti-diabetic treatment.
Grade 2 >160-250mg/dL or >8.9-13.9mmol/L	Initiate or intensify oral anti-diabetic treatment. Withhold capivasertib until fasting glucose (FG) level decrease to ≤160mg/dl (or ≤8.9mmol/L). If recovery occurs in ≤28 days, resume capivasertib at the same dose and maintain initiated or intensified anti-diabetic treatment. If improvement to ≤160mg/dL (or ≤8.9mmol/L) is reached in more than 28 days restart at one lower dose level and maintain initiated or intensified anti-diabetic treatment.
Grade 3 >250-500mg/dL or >13.9-27.8mmol/L	Withhold capivasertib until fasting glucose (FG) level decrease to ≤160mg/dl (or ≤8.9mmol/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 ≤160mg/dL (or ≤8.9mmol/L) within 28 days, restart capivasertib at one lower dose level and maintain initiated or intensified anti-diabetic treatment. If FG does not decrease to ≤160mg/dL (or ≤8.9mmol/L) within 28 days following appropriate treatment permanently discontinue capivasertib.
Grade 4 >500mg/dL or >27.8mmol/L)	Withhold capivasertib 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 ≤500mg/dl (or ≤27.8mmol/l) within 24 hours, then follow the guidance in the table for the relevant grade. If FG is confirmed at >500mg/dl (or ≥27.8mmol/l) after 24 hours, permanently discontinue capivasertib treatment.

Other toxicities

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

Hepatic impairment

Capivasertib

Mild hepatic impairment (bilirubin ≤ULN and AST >ULN or bilirubin >1.0x-1.5xULN).	No dose adjustment is required
Moderate hepatic impairment (bilirubin >1.5x-3.0xULN);	Limited data are available. Capivasertib should be administered to patients with moderate hepatic impairment only if the benefit outweighs the risk and these patients should be monitored closely for adverse effects due to potential increase in capivasertib exposure.
Severe hepatic impairment (bilirubin >3.0xULN),	Capivasertib is not recommended as safety and pharmacokinetics have not been studied in these patients.

Renal impairment

Capivasertib

Mild (CrCl 60 to 89mL/min) or moderate (creatinine clearance 30 to 59mL/min) renal impairment	No dose adjustment is required
Severe renal impairment (CrCl <30mL/min),	Capivasertib is not recommended as safety and pharmacokinetics have not been studied in these patients

Fulvestrant

No data for fulvestrant – use with caution

REFERENCES

1. SPC
2. CDF list