▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

TRUQAP®
Capivasertib

1 NAME OF THE MEDICINE

Capivasertib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRUQAP 160 mg: Each film-coated tablet contains 160 mg of capivasertib.

TRUQAP 200 mg: Each film-coated tablet contains 200 mg of capivasertib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet.

TRUQAP 160 mg tablets are round, biconvex, beige film-coated tablets debossed with 'CAV' above '160' on one side and plain on the reverse.

TRUQAP 200 mg tablets are capsule-shaped, biconvex, beige film-coated tablets debossed with 'CAV 200' on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRUQAP is indicated 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 following recurrence or progression on or after an endocrine based regimen.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with TRUQAP should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The recommended dose of TRUQAP in combination with fulvestrant is 400 mg (two 200 mg tablets) taken orally twice daily approximately 12 hours apart (total daily dose of 800 mg) with or without food, for 4 days followed by 3 days off treatment. See Table 1.

The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. Refer to the approved Product Information of fulvestrant for more information.

In pre/peri-menopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist according to current clinical practice standards.

For men, consider administering a LHRH agonist according to current clinical practice standards.

If a dose of TRUQAP is missed, it can be taken within 4 hours after the time it is usually taken. After more than 4 hours, the dose should be skipped. The next dose of TRUQAP should be taken at the usual time. There should be at least 8 hours between doses. If the patient vomits, an additional dose should not be taken. The next dose of TRUQAP should be taken at the usual time.

Table 1 TRUQAP dosing schedule for each week

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5***	**Day 6***	**Day 7***
Morning	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			
Evening	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			

*No dosing on day 5, 6 and 7.

Duration of treatment

Treatment with capivasertib should continue until disease progression or unacceptable toxicity occurs.

Dose adjustments

For Adverse Reactions

Treatment with TRUQAP may be interrupted to manage adverse reactions and dose reduction can be considered. Dose reductions for capivasertib should be carried out as described in Table 2. The dose of capivasertib can be reduced up to two times. Dose modification guidance for specific adverse reactions is presented in Tables 3-5.

Table 2 TRUQAP Dose reduction guidelines for adverse reactions

TRUQAP	**Dose and Schedule**	**Number and Strength of Tablets**
Starting dose	400 mg twice daily for 4 days followed by 3 days off treatment	Two 200 mg tablets
First dose reduction	320 mg twice daily for 4 days followed by 3 days off treatment	Two 160 mg tablets
Second dose reduction	200 mg twice daily for 4 days followed by 3 days off treatment	One 200 mg tablet

Hyperglycaemia

The optimal clinical management of hyperglycaemia has not been established. The following recommendations are based on limited clinical trial experience from the CAPItello-291 trial. Consultation with an endocrinologist should be considered and therapeutic management as per local guidelines. A potential for hypoglycaemia with antidiabetic medication administration on non-TRUQAP dosing days should be taken in account. In patients with risk factors for hyperglycaemia, consider monitoring fasting glucose more frequently as clinically indicated (see section 4.4 Special warnings and precautions for use).

Table 3 Recommended dose modification for TRUQAP for Hyperglycaemia

CTCAE Grade[a] and Fasting Glucose (FG)[b] values prior to TRUQAP dose	Recommendations[c]
Grade 1 > ULN-8.9 mmol/L or > ULN-160 mg/dL or HbA1C > 7%	• No TRUQAP dose adjustment required. • Consider initiation or intensification of oral anti-diabetic treatment.
Grade 2 > 8.9-13.9 mmol/L or > 160-250 mg/dL	• Withhold TRUQAP until FG decrease ≤ 8.9 mmol/L (or ≤ 160 mg/dL). • If FG does not decrease to ≤ 8.9 mmol/L (or ≤ 160 mg/dL) with treatment, withhold TRUQAP for up to 28 days until FG level decrease to ≤ 8.9 mmol/L (or ≤ 160 mg/dL). • If improvement to ≤ 8.9 mmol/L (or ≤ 160 mg/dL) is reached within 28 days, restart TRUQAP at the same dose level and maintain initiated or intensified anti-diabetic treatment. • If improvement to ≤ 8.9 mmol/L (or ≤ 160 mg/dL) is reached after 28 days restart at one lower dose level and maintain initiated or intensified anti-diabetic treatment.
Grade 3 > 13.9-27.8 mmol/L or > 250-500 mg/dL	• Withhold TRUQAP and consult an endocrinologist. • 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 ≤ 8.9 mmol/L (or ≤ 160 mg/dL) within 28 days restart TRUQAP at one lower dose level and maintain initiated or intensified anti-diabetic treatment. • If FG does not decrease to ≤ 8.9 mmol/L (or ≤ 160 mg/dL) within 28 days following appropriate treatment permanently discontinue TRUQAP.
Grade 4 > 27.8 mmol/L or > 500 mg/dL	• Withhold TRUQAP and consult with an endocrinologist. • 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 ≤ 27.8 mmol/L (or ≤ 500 mg/dL) within 24 hours, then follow the guidance in the table for the relevant grade. • If FG is confirmed at ≥ 27.8 mmol/L (or > 500 mg/dL) after 24 hours, permanently discontinue TRUQAP treatment.

[a] Grading according to NCI CTCAE Version 4.03

[b] Considerations should be also given to increases in HbA1C

[c] See Section 4.4 Special warnings and precautions for further recommendations on monitoring of glycaemia and other metabolic parameters

Diarrhoea
Consider secondary prophylaxis in patients with recurrent diarrhoea (see Section 4.4 Special warnings and precautions).

Table 4 Recommended dose modification for TRUQAP for Diarrhoea

CTCAE Grade[a]	Recommendations
Grade 1	• No TRUQAP 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 TRUQAP dose for up to 28 days until recovery to ≤ Grade 1 and resume TRUQAP dosing at same dose or one reduced dose level as clinically indicated. • If Grade 2 diarrhoea is persistent or recurring, maintain appropriate medical therapy and restart TRUQAP at the next lower dose level, as clinically indicated.
Grade 3	• Withhold TRUQAP • Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. • If the symptoms improve to ≤ Grade 1 in 28 days resume TRUQAP at one lower dose level. • If the symptom does not improve to ≤ Grade 1 in 28 days permanently discontinue TRUQAP
Grade 4	• Permanently discontinue TRUQAP.

[a] Grade according to the NCI CTCAE Version 5.0

Rash and other Skin drug reactions
Consider consultation with a dermatologist for all grades of skin drug reactions regardless of the severity. In patients with persistent rash and/or previous occurrence of grade 3 rash, consider secondary prophylaxis by continuing oral antihistamines and/or topical steroids.

Table 5 Recommended dose modification for TRUQAP for Rash and other Skin Drug Reactions

CTCAE Grade[a]	Recommendation
Grade 1	• No TRUQAP dose adjustment required. • Initiate emollients and consider adding oral non -sedating antihistamine treatment as clinically indicated to manage symptoms.
Grade 2	• Initiate or intensify topical steroid treatment and consider non-sedating oral antihistamines. • If no improvement with treatment, withhold TRUQAP. • Resume at the same dose level once the rash becomes clinically tolerable.
Grade 3	• Withhold TRUQAP. • Initiate appropriate dermatological treatment with topical steroid of moderate/ higher

CTCAE Grade[a]	Recommendation
	strength,-non-sedating oral antihistamines and /or systemic steroids. • If symptoms improve within 28 days to ≤ Grade 1, restart TRUQAP on one lower level. • If the symptoms do not improve to ≤ Grade 1 in 28 days discontinue TRUQAP • In patients with reoccurrence of intolerable ≥ Grade 3 rash, consider permanent discontinuation of TRUQAP.
Grade 4	• Permanently discontinue TRUQAP

[a] Grade according to the NCI CTCAE Version 5.0

Other toxicities

Table 6 Dose modification and management for other toxicities (excluding hyperglycaemia, diarrhoea and, skin drug reactions)

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

[a] Grading according to CTCAE Version 5.0

Co-administration with strong CYP3A4 inhibitors

Avoid concomitant use with a strong CYP3A4 inhibitor. If concomitant use cannot be avoided, reduce the dose of TRUQAP and monitor patients for adverse reactions. The dose of TRUQAP should be reduced to 320 mg twice daily (equivalent to a total daily dose of 640 mg) when co-administered with strong CYP3A4 inhibitors (see Section 4.5 Interactions with other medicines).

Special patient populations

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. TRUQAP is not recommended for patients with severe renal impairment, as safety and pharmacokinetics have not been studied in these patients (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. Limited data are available for patients with moderate hepatic impairment; TRUQAP should be administered to patients with moderate hepatic impairment only if the benefit outweighs the risk and these patients should be monitored closely for signs of toxicity. TRUQAP is not recommended for patients with

severe hepatic impairment, as safety and pharmacokinetics have not been studied in these patients (see Section 5.2 Pharmacokinetic properties).

Use in the elderly

No dose adjustment is required for elderly patients (see Section 5.2 Pharmacokinetic properties). There are limited data in patients aged ≥ 75 years.

Paediatric use

TRUQAP is not indicated for use in paediatric patients, as safety and efficacy of TRUQAP in children and adolescents have not been established.

Method of administration

TRUQAP tablets should be swallowed whole with water and not chewed, crushed dissolved, or divided. No tablets should be ingested if it is broken, cracked, or otherwise not intact.

4.3 CONTRAINDICATIONS

Prior severe hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperglycaemia

Severe hyperglycaemia has occurred in 8 (2.3%) patients treated with TRUQAP. Diabetic ketoacidosis was reported in one patient treated with TRUQAP in CAPItello-291. Before initiating treatment with TRUQAP, inform patients about TRUQAP's potential to cause hyperglycaemia and to immediately contact their healthcare professional if hyperglycaemia symptoms (e.g., excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss) occur. Patients should be tested for fasting blood glucose (FG) levels and HbA1C prior to treatment with capivasertib and at regular intervals during treatment. FG testing should be performed prior to the regular dose of TRUQAP. It is recommended to test FG at least every two weeks during the first month of treatment and at least once a month starting from the second month, and HbA1C every three months. More frequent FG testing is required in patients with medical history of 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, namely diabetic ketoacidosis. 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, TRUQAP dosing may be interrupted, reduced, or permanently discontinued (see Section 4.2 Dose and method of administration, Table 3).

The safety of TRUQAP in patients with Type 1 and Type 2 diabetes requiring insulin has not been studied as these patients were excluded from study. Patients with history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Diarrhoea

Severe diarrhoea associated with dehydration was observed in patients treated with TRUQAP. Acute kidney injury was reported in association with dehydration.

Diarrhoea has been frequently reported in patients treated with TRUQAP (see Section 4.8 Adverse effects).

Based on the severity of diarrhoea, TRUQAP dosing may be interrupted, reduced or permanently discontinued (see Section 4.2 Dose and method of administration, Table 4). Advise patients to start anti-diarrhoeal treatment at the first sign of diarrhoea, increase oral fluids if diarrhoea symptoms occur while taking TRUQAP. Maintenance of normovolemia and electrolyte balance is required in patients with diarrhoea to avoid complications related to hypovolemia and low electrolyte levels.

Rash and other skin reactions

Skin reactions, including erythema multiforme and dermatitis exfoliative generalised, were reported in patients receiving TRUQAP. Drug reaction with eosinophilia and systemic symptoms (DRESS) was reported in one patient treated with TRUQAP in CAPItello-291. Palmar-plantar erythrodysesthesia was reported in 3 patients treated with TRUQAP in CAPItello-291.

Patients should be monitored for signs and symptoms of rash or dermatitis and based on severity of skin drug reactions the dosing may be interrupted, reduced, or permanently discontinued (Section 4.2 Dose and method of administration, Table 5). Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

Patients excluded from the study

The patients with history of clinically significant cardiac disease including QTcF > 470 msec, any factors that increased the risk of QTc prolongation or risk of arrhythmic events or risk of cardiac function impairment were excluded from CAPItello 291. This should be considered if TRUQAP is prescribed in these patients.

Use in the elderly

No dose adjustment is required for elderly patients (see Section 5.2 Pharmacokinetic properties). There are limited data in patients aged ≥ 75 years.

Paediatric use

The safety and efficacy of TRUQAP in children aged 0-18 years of age has not been established.

Effects on laboratory tests

See Section 4.4 Special warnings and Precautions for use and Section 4.8 Adverse effects.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on capivasertib

In vitro studies have demonstrated that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Capivasertib is a substrate for P-glycoprotein (P-gp) and OCT2.

In a study in healthy subjects, co-administration of multiple 200 mg doses of the strong CYP3A4 inhibitor itraconazole with a single 80 mg capivasertib dose increased capivasertib AUC and C_{max} by 95% and 70%, respectively, relative to a single 80 mg capivasertib dose given alone. At the therapeutic dose regimen, the predicted increase in capivasertib AUC and C_{max} by itraconazole is between 52% and 56%, and between 30% and 35%, respectively, over a dosing cycle.

In a study in patients with prostate cancer, the strong CYP3A4 inducer enzalutamide decreased the capivasertib AUC by approximately 40% to 50% and rifampicin is predicted to decrease capivasertib AUC by approximately 70%.

Co-administration of a single dose of capivasertib 400 mg after repeated dosing of acid-reducing agent rabeprazole 20 mg twice daily for 3 days in healthy subjects did not result in clinically

relevant changes of the capivasertib exposure. The capivasertib AUC and C_{max} decreased by 6% and 27% respectively when administered with and without rabeprazole. In addition, a population pharmacokinetic analysis showed no significant impact of co-administration of acid reducing agents on the pharmacokinetics of capivasertib in patients. Capivasertib can be taken with acid reducing agents.

Based on physiologically based pharmacokinetic models, the predicted increase in capivasertib AUC by the moderate inhibitors verapamil and erythromycin is approximately 40%, with less impact on C_{max}. Co-administration with the UGT2B7 inhibitor probenecid is predicted to cause an increase in capivasertib AUC of 23 to 37% over a dosing cycle.

Effect of Other Drugs on TRUQAP

Table 7 Drug interactions with TRUQAP that affect capivasertib

Strong CYP3A4 inhibitors[a]	
Clinical impact	Concomitant use with a strong CYP3A4 inhibitor increases capivasertib concentration, which may increase the risk of TRUQAP toxicities (see Section 5.2 Pharmacokinetic properties).
Prevention or management	Avoid concomitant use with a strong CYP3A4 inhibitor. If concomitant use cannot be avoided, reduce the dose of TRUQAP and monitor patients for adverse reactions. TRUQAP (see Section 4.2 Dose and method of administration).
Examples[b]	Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole. Intake of high doses of grapefruit should be avoided.
Moderate CYP3A4 inhibitors	
Clinical impact	Concomitant use with a moderate CYP3A4 inhibitor is predicted to increase capivasertib concentration, which may increase the risk of TRUQAP toxicities (See section 5.2 Pharmacokinetic properties)
Prevention or management	When concomitantly used with moderate CYP3A4 inhibitor, reduce the dose of TRUQAP and monitor patients for adverse reactions (see Section 4.2 Dose and method of administration).
Strong CYP3A4 inducers[c]	
Clinical impact	Concomitant use with a strong CYP3A4 inducer decreases capivasertib concentration which may reduce the efficacy of TRUQAP (see Section 5.2 Pharmacokinetic properties).
Prevention or management	Concomitant use of strong CYP3A4 inducers is not recommended.
Examples[b]	Carbamazepine, phenytoin, rifampicin, St. John’s wort.

Moderate CYP3A4 inducers[d]	
Clinical Impact	There is a potential for decreased capivasertib concentration when TRUQAP is concomitantly used with moderate CYP3A4 inducers. This may reduce the efficacy of TRUQAP.
Prevention or management	Moderate CYP3A4 inducers should be used with caution with TRUQAP.
Examples[b]	Bosentan, cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, modafinil, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine.

[a] Strong inhibitors increase the AUC of sensitive substrates for CYP3A4 (e.g. midazolam) ≥ 5-fold.

[b] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[c] Strong inducers decrease the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) by ≥ 80%.

[d] Moderate inducers decrease the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) by ≥ 50% to < 80%.

Effects of capivasertib on other medicinal products

Co-administration of TRUQAP at the recommended dose with midazolam (CYP3A substrate), increased the AUC of midazolam by 15% on the 3rd off-dosing day and by 77% on the 4th on-dosing day of capivasertib which shows that capivasertib is a weak CYP3A inhibitor.

Capivasertib inhibited CYP2C9, CYP2D6, CYP3A4 and UGT1A1 metabolising enzymes and BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K drug transporters in *in vitro* studies. Capivasertib induced CYP3A4 *in vitro* in human hepatocytes.

Based on *in vitro* data and physiologically based modelling, capivasertib was predicted to have no effect on the AUC of CYP2C9, CYP2D6 or UGT1A1 substrates, atorvastatin or rosuvastatin.

Effect of TRUQAP on Other Drugs

Table 8 Drug interactions with TRUQAP that may affect other drugs

Substrates of CYP3A	
Clinical impact	Concentration of drugs that are primarily eliminated via CYP3A metabolism may be increased by concomitant use with TRUQAP. This may result in increased toxicity of these drugs, depending on their therapeutic window.
Prevention or management	Dose adjustment may be required for drugs that are primarily eliminated via CYP3A metabolism and have a narrow therapeutic window. Refer to specific guidance in the prescribing information for these drugs.
Examples[a]	Carbamazepine, ciclosporin, fentanyl, pimozide, simvastatin, tacrolimus.
Interactions with hepatic transporters (OATP1B1, OATP1B3)	
Clinical impact	The concentration of drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3 if they are metabolised by CYP3A4, may increase by concomitant use with TRUQAP (see Section 5.2 Pharmacokinetic properties). This may result in increased toxicity.

Prevention or management	Depending on their therapeutic window, dose adjustment may be required for drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3, if they are metabolised by CYP3A4. Refer to specific guidance in the prescribing information for these drugs.
Examples[a]	Simvastatin
Interactions with renal transporters (MATE1, MATE2K, OCT2)	
Clinical impact	The concentration of drugs that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by concomitant use with TRUQAP (see Section 5.2 Pharmacokinetic properties). This may result in increased toxicity. Transient serum creatinine increases may be observed during treatment with TRUQAP due to inhibition of OCT2, MATE1 and MATE2K by capivasertib.
Prevention or management	Depending on their therapeutic window, dose adjustment may be needed for drugs that are sensitive to inhibition of MATE1, MATE2K, OCT2. Refer to specific guidance in the prescribing information for these drugs.
Examples[a]	Dofetilide, procainamide.

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no clinical data on fertility. In repeat-dose toxicity studies, capivasertib resulted in tubular degeneration in the testes and cellular debris and decreased spermatocytes in the epididymides in mice, rats and dogs at oral doses of 150, 100 and 15 mg/kg/day, respectively (exposure similar to the clinical exposure in humans based on AUC). Capivasertib had no effects on fertility in male rats at doses up to 100 mg/kg/day for 10 weeks. The effect on female fertility in animals has not been studied.

Use in pregnancy – Category D

There are no data from the use of TRUQAP in pregnant women. Studies in animals have shown reproductive toxicity. In a rat embryo fetal study, capivasertib caused an increase in post implantation loss, an increase in early embryonic deaths, together with reduced gravid uterine and fetal weights, and minor fetal visceral variations (left sided umbilical artery). These effects were seen at a dose level of 150 mg/kg/day which caused maternal toxicity, and where plasma concentrations were approximately 0.8 times the exposure in humans at the recommended dose of 400 mg twice daily (based on total AUC). When capivasertib was administered to pregnant rats at 150 mg/kg/day throughout gestation and through early lactation, there was a reduction in litter and pup weights. PI3K/AKT/mTOR signalling plays important roles in embryofetal development. A range of growth defects were seen in Akt knockout mice. Therefore, TRUQAP is not recommended during pregnancy and in women of childbearing potential not using contraception.

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TRUQAP. A pregnancy test should be performed for women of childbearing potential prior to initiating treatment, and verified as negative prior to initiating treatment, and re-testing considered throughout treatment.

Patients should be advised to use effective contraception during treatment with TRUQAP and for the following periods after completion of treatment with TRUQAP: at least 4 weeks for females and 16 weeks for males.

Please refer to Section 4.6 Fertility, Pregnancy and Lactation of the approved Product Information for fulvestrant.

Use in lactation

It is not known whether capivasertib or its metabolites are excreted in human milk. Exposure to capivasertib was confirmed in suckling rat pups which may indicate the excretion of capivasertib in milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with TRUQAP.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

During treatment with capivasertib, fatigue has been reported and those patients who experience this symptom should be advised to observe caution when driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Overall summary of the safety profile

Severe hyperglycaemia, diarrhoea, and skin reactions have occurred in patients taking capivasertib (see Section 4.4 Special warnings and precautions for use).

The safety profile of TRUQAP is based on data from 355 patients who received TRUQAP plus fulvestrant in CAPItello-291.

The most common adverse reactions (reported at a frequency of ≥ 20%), were diarrhoea (72.4%), rash (40.3%), nausea (34.6%), fatigue (20.8%) and vomiting (20.6%). The most common grade 3 or 4 adverse reactions (reported at frequency ≥ 2%) were rash (12.4%), diarrhoea (9.3%), hyperglycaemia (2.3%), anaemia (2.0%), and stomatitis (2.0%).

Serious adverse reactions (SARs) were seen in 23 (6.5%) patients receiving TRUQAP plus fulvestrant. Serious adverse reactions reported in ≥ 1% of patients receiving TRUQAP plus fulvestrant included rash 8 (2.3%), diarrhoea 6 (1.7%), and vomiting 4 (1.1%).

Dose reductions due to adverse reactions were reported in 62 (17.5%) patients. The most common adverse reactions (reported at frequency ≥ 1%) leading to dose reduction of TRUQAP were diarrhoea (7.9%) and rash (4.5%).

Treatment discontinuation due to adverse reactions occurred in 33 (9.3%) patients. The most common adverse reactions (reported at frequency ≥ 1%) leading to treatment discontinuation were rash (4.5%), diarrhoea (2.0%), and vomiting (2.0%).

Fatal adverse events regardless of causal association with TRUQAP occurred in 4 (1.1%) of patients who received TRUQAP with fulvestrant, including 1 (0.3%) pneumonia aspiration, 1 (0.3%) sepsis, 1 (0.3%) cerebral haemorrhage and 1 (0.3%) acute myocardial infarction.

Adverse Drug Reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 9 Adverse drug reactions in Patients who Received TRUQAP with Fulvestrant in CAPItello-291

		TRUQAP with Fulvestrant N=355		Placebo with Fulvestrant N=350	
MedDRA SOC	**MedDRA Term**	**Any Grade (%)**	**Grade 3 or 4 (%)**	**Any Grade (%)**	**Grade 3 or 4 (%)**
Infections and infestations	Urinary Tract Infection[1]	48 (13.5)	6 (1.7)	24 (6.9%)	0
Blood and lymphatic system disorders	Anaemia	37 (10.4)	7 (2.0)	17 (4.9%)	4 (1.1)
Immune system disorders	Hypersensitivity[2]	3 (0.8)	0	0	0
Metabolism and nutrition disorders	Hyperglycaemia[3]	60 (16.9)	8 (2.3)	14 (4.0 %)	1 (0.3)
	Decreased appetite	59 (16.6)	1 (0.3)	22 (6.3)	2 (0.6)
Nervous system disorders	Dysgeusia	21 (5.9)	0	4 (1.1)	0
Gastrointestinal disorders	Diarrhoea[4]	257 (72.4)	33 (9.3)	70 (20)	1 (0.3)
	Nausea	123 (34.6)	3 (0.8)	54 (15.4)	2 (0.6)
	Vomiting	73 (20.6)	6 (1.7)	17 (4.9)	2 (0.6)
	Stomatitis[5]	61 (17.2)	7 (2.0)	19 (5.4)	0
	Dyspepsia	18 (5.1)	0	7 (2.0)	0
Skin and subcutaneous tissue disorders	Rash[6]	143 (40.3)	44 (12.4)	29 (8.3)	1 (0.3)
	Pruritis	44 (12.4)	2 (0.6)	23 (6.6)	0
	Dry skin	25 (7.0)	0	15 (4.3)	1 (0.3)
	Erythema multiforme	6 (1.7)	3 (0.8)	0	0
	Drug Eruption	4 (1.1)	4 (1.1)	0	0
	Dermatitis	3 (0.8)	0	1 (0.3)	0
	Dermatitis exfoliative generalised	2 (0.6)	2 (0.6)	0	0
	Toxic Skin Eruption	1 (0.3)	0	0	0
General disorders and administration site conditions	Fatigue	74 (20.8)	2 (0.6)	45 (12.9)	2 (0.6)
	Mucosal inflammation	11 (3.1)	1 (0.3)	1 (0.3)	0
Investigations	Blood creatinine increased	16 (4.5)	1 (0.3)	2 (0.6)	0
	Glycosylated haemoglobin increased	5 (1.4)	0	0	0

[1] Urinary Tract Infection includes urinary tract infection and cystitis.

[2] Hypersensitivity includes hypersensitivity and drug hypersensitivity.

[3] Hyperglycaemia includes hyperglycaemia and blood glucose increased.

[4] Diarrhoea includes diarrhoea and frequent bowel movements.

[5] Stomatitis includes stomatitis, aphthous ulcer and mouth ulceration.

[6] Rash includes erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic.

Description of selected adverse reaction

Hyperglycaemia

Hyperglycaemia of any grade occurred in 60 (16.9%) patients and grade 3 or 4 occurred in 8 (2.3%) patients receiving TRUQAP. In the study, dose reduction was required in 2 (0.6%) patients and 1 (0.3%) patient discontinued treatment due to hyperglycaemia. In the 60 patients with hyperglycaemia, 28 (46.7%) patients were treated using anti-hyperglycaemic medication including insulin in 10 (16.7%) patients, metformin in 18 (30%) patients and 10 (16.7%) patients were on other anti-hyperglycaemic medication. Some patients may have received more than one anti-hyperglycaemic medication.

Of the 60 patients with hyperglycaemia, in 37 (61.6%) patients hyperglycaemia improved or resolved at treatment discontinuation or last follow up.

Diarrhoea

Diarrhoea occurred in 257 (72.4%) patients receiving TRUQAP. Grade 3 and/or 4 diarrhoea occurred in 33 (9.3%) patients. Dose reduction was required in 28 (7.9%) patients and 7 (2.0%) patients discontinued TRUQAP due to diarrhoea. In the 257 patients with diarrhoea, anti-diarrheal medication was required in 59% (151/257) of patients to manage diarrhoea symptoms.

Rash

Rash (including erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic) was reported in 143 (40.3%) patients. Grade 3 and/or 4 occurred in 44 (12.4%) of patients who received capivasertib. Dose reduction was required in 16 (4.5%) patients and 16 (4.5%) patients discontinued TRUQAP due to rash.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is currently no specific treatment in the event of an overdose with TRUQAP and possible symptoms of overdose are not established. Physicians should follow general supportive measures and patients should be treated symptomatically.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Capivasertib is an inhibitor of the kinase activity of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). AKT is a pivotal node in the phosphatidylinositol 3-kinase (PI3K)

signalling cascade regulating multiple cellular processes including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. AKT activation in tumours is a result of upstream activation from other signalling pathways, mutations of AKT, loss of Phosphatase and Tensin Homolog (PTEN) function and mutations in the catalytic subunit of PI3K (PIK3CA).

Capivasertib inhibits the phosphorylation of AKT substrates such as glycogen synthase kinase 3-β (GSK3β) and proline-rich AKT substrate of 40 kilodaltons (PRAS40). Capivasertib reduces growth of a range of cell lines derived from solid tumours and haematological disease. Multiple breast cancer cell lines were sensitive to capivasertib monotherapy. Within cell lines showing greater sensitivity to capivasertib there was an enrichment of PIK3CA or AKT1 mutations, or loss of PTEN. Some cell lines lacking such mutations were also sensitive to capivasertib.

In vivo, monotherapy, capivasertib inhibits growth of human cancer xenograft models representative of different tumour types. including ER^+ and triple negative breast cancer models with *PIK3CA*, *AKT1* mutations, *PTEN* loss and HER2 amplification, mutant xenograft models and triple negative breast cancer xenograft models. Combined treatment with capivasertib and fulvestrant demonstrated a greater anti-tumour response in a range of human breast cancer PDX models representative of different breast cancer subsets. This included models without detectable mutations or alterations in *PIK3CA*, *PTEN* or *AKT*, as well as models with mutations or alterations in *PIK3CA*, *PTEN* or *AKT*.

Cardiac Electrophysiology

Based on an exposure-response modelling analysis of data from 180 patients with advanced solid malignancies who received capivasertib doses from 80 to 800 mg a linear relationship between capivasertib concentration and increases in the QTcF interval was projected. The estimated QTcF prolongation was 3.87 ms at the steady state C_{max} following 400 mg twice daily and the exposure that is predicted to cause a QTcF prolongation of 20 ms is approximately 4- to 5-fold higher than the therapeutic C_{max}. No clinically relevant effect of capivasertib on QT prolongation associated with pro-arrhythmic effect was observed at the recommended dose of 400 mg twice daily in the pivotal study. Patients with QTcF >470 were not included in CAPItello-291.

Clinical trials

CAPItello-291 was a randomised, double-blind, placebo-controlled study designed to demonstrate the efficacy and safety of TRUQAP in combination with fulvestrant in adult females, pre- or post-menopausal, and adult males with locally advanced (inoperable) or metastatic HR positive and HER2 negative breast cancer following recurrence or progression on or after aromatase inhibitor (AI) based treatment. The trial enrolled 708 adult patients with locally advanced (inoperable) or metastatic HR-positive, HER2-negative breast cancer irrespective of *PIK3CA/AKT1/PTEN*-alteration status.

PIK3CA/AKT1/PTEN alteration status was identified centrally and retrospectively by Next Generation Sequencing (NGS) using the FoundationOne® CDx assay, excluding in China where a Burning Rock Oncoscreen Plus assay was used, and classified in accordance with the principles published in the American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants.

Patients with qualifying alterations in *PIK3CA/AKT1/PTEN* genes were included in the analyses for the overall population and the *PIK3CA/AKT1/PTEN* altered subgroup. 289 (40.8%) patients, 155 (43.7%) in capivasertib arm and 134 (38.0%) in the placebo arm met these criteria.

A total of 313 patients (44.2%) had tumours that did not harbour qualifying mutations in the *PIK3CA/AKT1/PTEN* genes. 142 (40.0%) of patients included in the capivasertib treatment arm and 171 (48.4%) in the placebo arm met these criteria.

Of the 106 patients (15% of total study participants) with unknown *PIK3CA/AKT1/PTEN* alteration status, 14 (13%) were unknown due to no sample availability, 73 (69%) because of preanalytical failure, and 19 (18%) because of post analytical failure.

Patients were to have received treatment with an AI-containing regimen (single agent or in combination) and have:

- Radiological evidence of breast cancer recurrence or progression while on, or within 12 months of the end of (neo)adjuvant treatment with an AI, or
- Radiological evidence of progression while on prior AI administered as a treatment line for locally advanced or metastatic breast cancer (this did not need to be the most recent therapy).

Patients were excluded if they had more than 2 lines of endocrine therapy for locally advanced (inoperable) or metastatic disease, more than 1 line of chemotherapy for locally advanced (inoperable) or metastatic disease, prior treatment with AKT, PI3K, mTOR inhibitors, fulvestrant and/or other SERDs, clinically significant abnormalities of glucose metabolism (defined as patients with diabetes mellitus Type 1 or Type 2 requiring insulin treatment, and/or HbA1c≥8.0% (63.9 mmol/mol)), history of clinically significant cardiac disease, and symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy.

A total of 708 patients were randomised 1:1 to receive either 400 mg of TRUQAP (N=355) or placebo (N=353) given twice daily for 4 days followed by 3 days off treatment each week of 28-day treatment cycle. Fulvestrant 500 mg was administered on cycle 1 days 1 and 15 and then at day 1 of a 28-day cycle. Peri/pre-menopausal women were treated with an LHRH agonist. Randomisation was stratified by presence of liver metastases, prior treatment with CDK4/6 inhibitors and geographical region (region 1: US, Canada, Western Europe, Australia and Israel vs region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. A tumour sample was collected prior to randomisation to determine *PIK3CA/AKT1/PTEN* alteration status retrospectively by central testing.

Demographic and baseline characteristics were well balanced between arms. Of the 708 patients, the median age was 58 years (range 26 to 90); female (99%); White (57.5%), Asian (26.7%), Black (1.1%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (65.7%), 1 (34.2%), 21.8% were pre/peri menopausal. All patients received prior endocrine-based therapy (100% AI based treatment and 44.1% received tamoxifen). Prior treatment with CDK4/6 inhibitor was reported in 70.1% of patients. Chemotherapy for locally advanced (inoperable) or metastatic disease was reported in 18.2% of patients. Patient demographics for those in the PIK3CA/AKT1/PTEN-altered subgroup were generally representative of the overall study population.

The dual primary endpoints were investigator assessed progression free survival (PFS) in the overall population and PFS in the PIK3CA/AKT1/PTEN-altered subgroup per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The key secondary endpoints of overall survival (OS) and objective response rate (ORR) will be formally analysed at future data cut offs.

At the time of primary analysis, the median duration of follow-up for PFS in the overall population was 13 months (range: 0 to 25 months) in censored patients.

The study demonstrated statistically significant and clinically meaningful improvement in PFS for patients receiving TRUQAP plus fulvestrant compared to patients receiving placebo plus fulvestrant, in both the overall population and the PIK3CA/AKT1/PTEN-altered subgroup. An exploratory analysis of PFS in the 313 (44%) patients in the Known Non-altered Population (no PIK3CA/AKT1/PTEN altered tumour) showed a HR (95% CI) of 0.79 (0.61 to 1.02). The median

PFS (95% CI) was 5.3 months (3.6 to 7.3) in the capivasertib group compared with 3.7 months (3.5 to 5.1) in the placebo group. An exploratory analysis of PFS in the 106 (15%) patients in the No Result Population showed a HR (95% CI) of 0.52 (0.32 to 0.83). The median PFS (95% CI) was 10.0 months (7.3 to 11.1) in the capivasertib group compared with 1.9 months (1.8 to 7.3) in the placebo group. PFS results by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. Scans were repeated every 8 weeks (±7 days) for the first 18 months and every 12 weeks (±7 days) thereafter, after start of treatment until objective radiological disease progression as defined by RECIST v1.1.

A preliminary assessment of OS in the overall population (28% maturity) and altered population (30% maturity) at the time of the primary PFS analysis does not suggest a detrimental effect on survival of treatment with capivasertib plus fulvestrant compared with placebo plus fulvestrant. The investigator-assessed ORR in patients receiving TRUQAP plus fulvestrant and placebo plus fulvestrant was 22.9% and 12.2%, respectively, in the overall population and 28.8% and 9.7%, respectively, in the altered subgroup. The investigator-assessed ORR in patients receiving capivasertib plus fulvestrant and placebo plus fulvestrant was 17.1% and 14.5%, respectively, in the Known Non-altered Population and 22.4% and 11.4%, respectively, in the unknown subgroup.

Efficacy results for overall population and PIK3CA/AKT1/PTEN-altered subgroup are presented in Table 10 and Figure 1 and Figure 2.

Table 10 Progression-free Survival, by Investigator Assessment

	Overall population N = 708		**PIK3CA/AKT1/PTEN altered subgroup N = 289**		**Confirmed non-altered subgroup N=313**		**Unknown subgroup N=106**	
	TRUQAP plus fulvestrant N = 355	**Placebo plus fulvestrant N = 353**	**TRUQAP plus fulvestrant N = 155**	**Placebo plus fulvestrant N = 134**	**TRUQAP plus fulvestrant N = 142**	**Placebo plus fulvestrant N = 171**	**TRUQAP plus fulvestrant N = 58**	**Placebo plus fulvestrant N = 48**
Number of PFS events – n (%)	258 (72.7)	293 (83.0)	121 (78.1)	115 (85.8)	103 (72.5)	141 (82.5)	34 (58.6)	37 (77.1)
Median PFS months (95% CI)	7.2 (5.5, 7.4)	3.6 (2.8, 3.7)	7.3 (5.5, 9.0)	3.1 (2.0, 3.7)	5.3 (3.6, 7.3)	3.7 (3.5, 5.1)	10.0 (7.3, 11.1)	1.9 (1.8, 7.3)
Hazard ratio (95% CI)[a]	0.60 (0.51, 0.71)		0.50 (0.38, 0.65)		0.79 (0.61, 1.02)		0.52 (0.32, 0.83)	
p-value[b]	<0.001		<0.001		NA		NA	

[a] Stratified Cox proportional hazards model. A hazard ratio < 1 favours capivasertib + fulvestrant. For the Overall population, log-rank test and Cox model stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no) and geographic region (Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia). For the altered population, the log-rank test and Cox model stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no).

[b] Stratified log-rank test.

Figure 1 **Kaplan-Meier Plot of Progression-Free Survival in CAPItello-291 (Investigator Assessment, Overall population)**

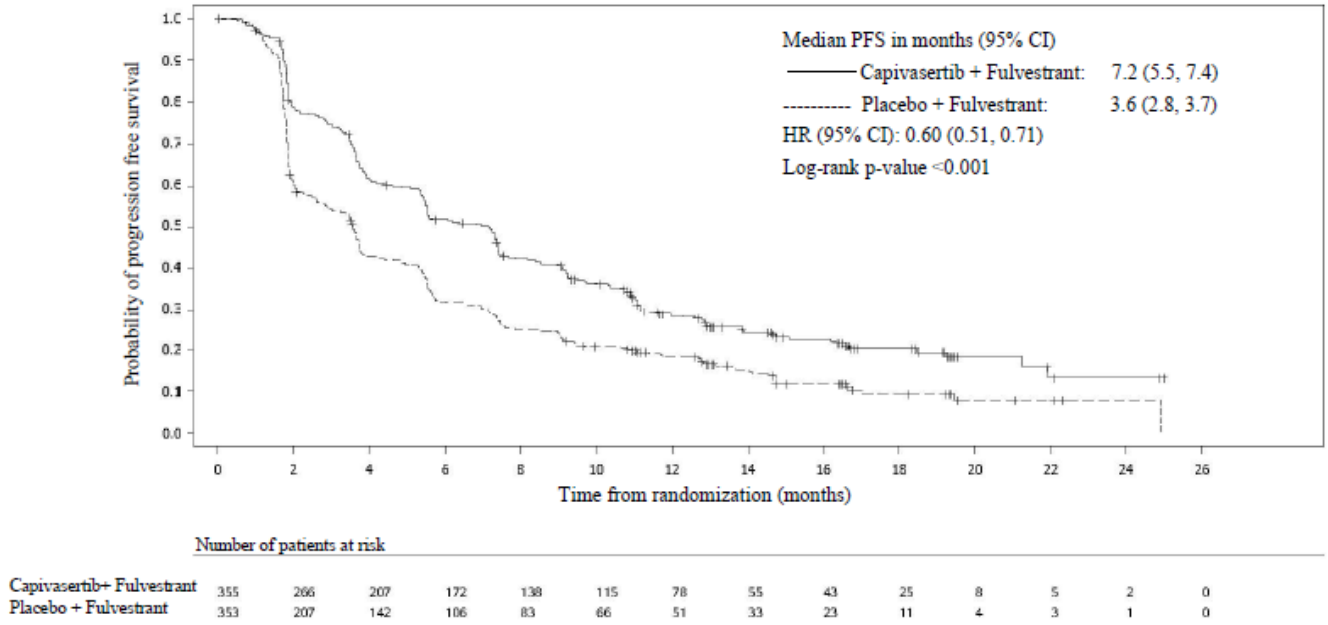
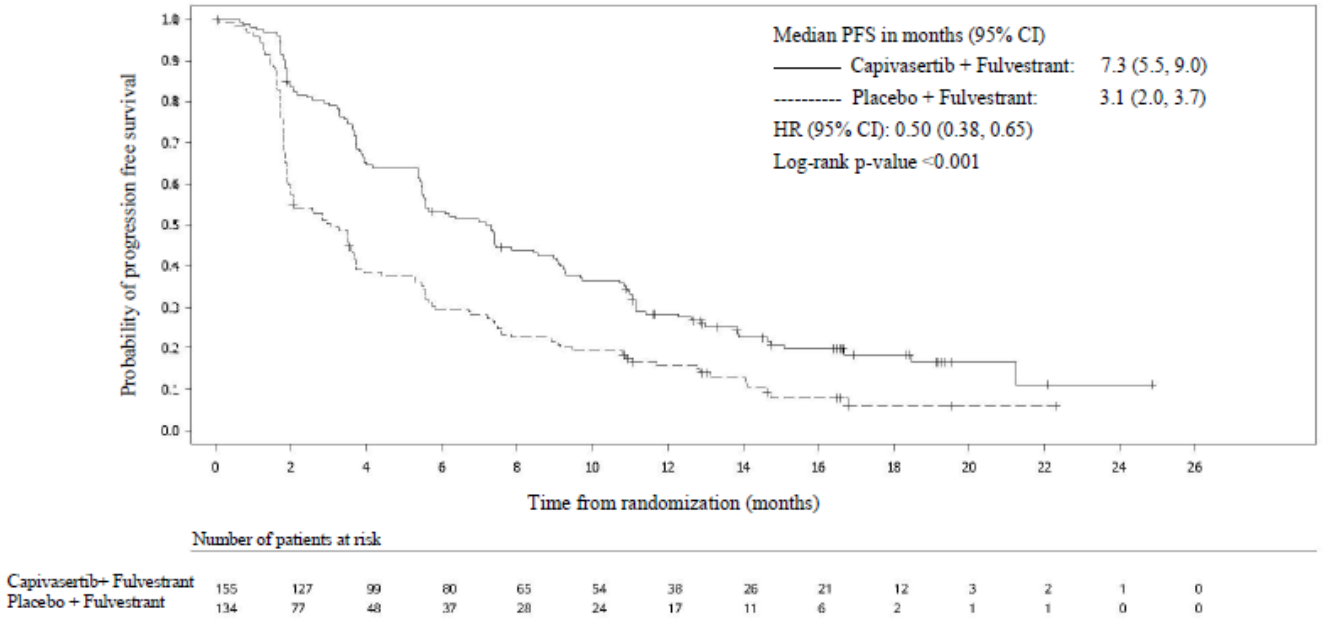


Figure 2 **Kaplan-Meier Plot of Progression-Free Survival in CAPItello-291 (Investigator Assessment, PIK3CA/AKT1/PTEN-altered subgroup)**



Improvement in PFS in the overall population and in patients with *PIK3CA/AKT1/PTEN*-altered tumours treated with TRUQAP plus fulvestrant was observed across all pre-specified subgroups, including prior exposure to CDK4/6 inhibitors.

5.2 PHARMACOKINETIC PROPERTIES

Capivasertib pharmacokinetics have been characterised in healthy subjects and patients with solid tumours. The systemic exposure (AUC and C_{max}) increased approximately proportionally to the

dose over the 80 to 800 mg dose range when given to patients. Following intermittent dosing of capivasertib 400 mg twice daily, 4 days on, 3 days off, steady-state levels are predicted to be attained on every 3rd and 4th dosing day each week, starting from week 2. During the off-dosing days, the plasma concentrations are low (approximately 0.5% to 15% of the steady state C_{max}).

Absorption

Capivasertib is rapidly absorbed with peak concentration (C_{max}) observed at approximately 1-2 hours in patients. The mean absolute bioavailability is 29%.

Food Effect

When capivasertib was administered after a high-fat, high-calorie meal (approximately 1000 kcal), the fed to fasted ratio was 1.32 and 1.23, for AUC and C_{max}, respectively, compared to when given after an overnight fast. When capivasertib was administered after a low-fat, low-calorie (approximately 400 kcal), the exposure was similar to that after fasted administration with fed to fasted ratios of 1.14 and 1.21, for AUC and C_{max}, respectively. Co-administration with food did not result in clinically relevant changes to the exposure.

Distribution

The mean volume of distribution (V_{ss}) was 205 L after intravenous administration to healthy subjects. Capivasertib is not extensively bound to plasma protein (percentage unbound 22%) and the plasma to blood ratio is 0.71.

Metabolism

Capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. The major metabolite in human plasma was an ether glucuronide that accounted for 83% of total drug-related material. A minor oxidative metabolite was quantified at 2% and capivasertib accounted for 15% of total circulating drug-related material. No active metabolites have been identified.

Excretion

The effective half-life after multiple dosing in patients was 8.3 hours. The mean total plasma clearance was 38 L/h after a single intravenous administration to healthy subjects. The mean total oral plasma clearance was 60 L/h after single oral administration and decreased by 8% after repeated dosing of 400 mg twice daily.

Following single oral dose of 400 mg, the mean total recovery of radioactive dose was 45% from urine and 50% from faeces. Renal clearance was 21% of total clearance. Capivasertib is primarily eliminated by metabolism.

<u>Special populations</u>

Effect of race, age, gender and weight

There were no clinically significant differences in pharmacokinetics of capivasertib based on race/ethnicity (including White and Asian patients), gender or age. There was a statistically significant correlation of apparent oral clearance of capivasertib to body weight. Compared to a patient with a body weight of 66 kg, a 47 kg patient is predicted to have 12% higher AUC. There is no basis for dose modification based on body weight as the predicted effect on capivasertib exposure was small.

Renal impairment

Based on population pharmacokinetic analyses, AUC and C_{max} were 1% higher in patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), compared to patients with normal

renal function. AUC and C_{max} were 16% higher in patients with moderate renal impairment (creatinine clearance 30 to 59 mL/min), compared to patients with normal renal function.

There is no data in severe renal impairment or end-stage renal disease (creatinine clearance < 30 mL/min).

Hepatic impairment

Based on population pharmacokinetic analyses, AUC and C_{max} were 5% higher in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1 ULN to ≤ 1.5 ULN), compared to patients with normal hepatic function. No dose adjustment is required for patients with mild hepatic impairment.

Based on limited data the AUC and C_{max} was 17% and 13% higher respectively in patients with moderate hepatic impairment (bilirubin > 1.5 ULN to ≤ 3 ULN), compared to patients with normal hepatic function. There is limited data in patients with moderate hepatic impairment and no data in severe hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Capivasertib showed no mutagenic or genotoxic potential *in vitro*. Capivasertib was not mutagenic in a bacterial reverse mutation (Ames) assay, or genotoxic in mouse lymphoma cells *in vitro*. In rats treated orally with doses of 150 mg/kg/day, capivasertib induced micronuclei in the bone marrow via an aneugenic mode of action. These findings occurred at plasma concentrations similar to those observed in humans at the maximum recommended clinical dose of 400 mg twice daily (based on C_{max} or AUC).

Carcinogenicity

Carcinogenicity studies have not been conducted with capivasertib.

Non-clinical/Repeat-dose toxicity

The major target organs or systems for toxicity were insulin signalling (increased levels of glucose and insulin in mice, rats and dogs), the male reproductive organs (tubular degeneration in mice, rats and dogs), and the renal system in rats (polyuria, decreased tubular epithelial cell size, decreased kidney size and weight). The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing. Findings occurred at plasma concentrations lower or similar to those in humans (approximately 0.14 to 2 times) at the recommended dose of 400 mg twice daily (based on total AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: microcrystalline cellulose, calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate

Tablet coating: hypromellose, titanium dioxide, macrogol 3350, polydextrose, copovidone, medium chain triglycerides, iron oxide black, iron oxide red, iron oxide yellow

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Capivasertib 160 mg and 200 mg film-coated tablets are supplied in aluminium/aluminium blisters containing 16 tablets. Each pack contains 64 tablets (4 blisters).

*not all presentations may be available in Australia.

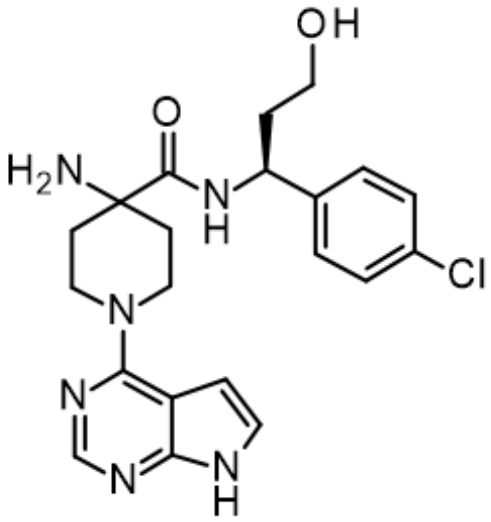
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Figure 3 Chemical structure/General structure of capivasertib



CAS number

1143532-39-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

09 May 2024

10 DATE OF REVISION

Not applicable.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product

VV-RIM-06044278 v1.0