PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF MEDICINE

TRUQAP® 160 mg film-coated tablets

TRUQAP® 200 mg film-coated tablets

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.

Contains sugar: polydextrose (2,40mg/160 mg tablet; 2,87 mg/200 mg tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

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 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 estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer with one or more

PIK3CA/AKT1/PTEN-alterations as detected by an approved test following progression on at least one endocrine-based regimen.

In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

For men with breast cancer, administration of LHRH agonist according to current clinical practice standards should be considered.

4.2 Posology and method of administration

Treatment with TRUQAP should be initiated and supervised by a medical practitioner experienced in the use of anticancer medicines.

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

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

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

Refer to the approved Professional Information of fulvestrant for more information.

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.

Duration of treatment

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

Dose adjustments

Treatment with TRUQAP may be interrupted to manage adverse reactions and dose reduction can be considered. If dose reduction is considered, the dose reduction guidelines are described in Table 2. The dose of TRUQAP 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

Consider a consult with an endocrinologist when selecting the antidiabetic medicinal product, a potential for hypoglycaemia with antidiabetic medication administration on non-TRUQAP dosing days should be taken in account.

Table 3 Recommended dose modification of TRUQAP for Hyperglycaemia[a]

CTCAE Grade[b] and Fasting Glucose (FG)[c] values prior to TRUQAP dose	**Recommendations[d]**
Grade 1 > ULN - 160 mg/dL or > ULN – 8,9 mmol/L or HbA1C > 7 %	No TRUQAP 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 without dose adjustment of TRUQAP. If FG does not decrease to ≤ 160 mg/dl (or ≤ 8,9 mmol/L) with treatment, interrupt

	TRUQAP for up to 28 days until FG level decrease to ≤ 160 mg/dL (or ≤ 8,9 mmol/L). If improvement to ≤ 160 mg/dL (or ≤ 8,9 mmol/L) is reached within 28 days, restart TRUQAP at the same dose level and maintain initiated or intensified anti-diabetic treatment. If improvement to ≤ 160 mg/dL (or ≤ 8,9 mmol/L) is reached after 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 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 ≤ 160 mg/dL (or ≤ 8.9 mmol/L) within 28 days restart TRUQAP 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 TRUQAP.
Grade 4 > 500 mg/dL or > 27,8 mmol/L	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 ≤ 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 TRUQAP treatment.

[a]For the management of suspected or confirmed DKA refer to Section 4.4.

[b] Grading according to NCI CTCAE Version 4.03.

[c] Considerations should be also given to increases in HbA1C.

[d] See section 4.4 Special warnings and special precautions for further recommendations on monitoring of glycaemia and other metabolic parameters.

Diarrhoea

Consider secondary prophylaxis in patients with recurrent diarrhoea.

Table 4 Recommended dose modification of 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. Interrupt TRUQAP dose for up to 28 days until recovery to ≤ Grade 1 and resume TRUQAP 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 TRUQAP at one lower dose level, as clinically indicated.
Grade 3	Interrupt 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 symptoms do not improve to ≤ Grade 1 in 28 days permanently discontinue TRUQAP.
Grade 4	Permanently discontinue TRUQAP.

[a] Grading according to NCI CTCAE Version 5.0.

Rash and other Skin Reactions

Consider consultation with a dermatologist for all grades of skin 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 of TRUQAP for rash and other skin reactions

CTCAE Grade[a]	**Recommendations**
Grade 1	No TRUQAP dose adjustment required.

	Initiate emollients and consider adding an oral nonsedating 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, interrupt TRUQAP. Resume at the same dose level once the rash becomes clinically tolerable.
Grade 3	Interrupt TRUQAP. Initiate appropriate dermatological treatment with topical steroid of moderate/ higher strength, nonsedating oral antihistamines and /or systemic steroids. If symptoms improve within 28 days to ≤ Grade 1, restart TRUQAP on one lower dose 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] Grading according to NCI CTCAE Version 5.0.

Other toxicities

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

CTCAE Grade[a]	**Recommendation**

Grade 1	No TRUQAP dose adjustment required, initiate appropriate medical therapy, and monitor as clinically indicated.
Grade 2	Interrupt TRUQAP until symptoms improve to ≤ Grade 1
Grade 3	Interrupt 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

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).

Special populations

Elderly

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

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).

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).

Paediatric population

TRUQAP is not indicated for use in paediatric patients (see section 4.8).

Method of administration

TRUQAP tablets should be swallowed whole with water and not chewed, crushed, dissolved, or divided. TRUQAP should not be ingested if it is broken, cracked, or otherwise not intact.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hyperglycaemia

Severe hyperglycaemia, associated with diabetic ketoacidosis (DKA) and ketoacidosis, was reported in patients treated with TRUQAP (see section 4.8). Some cases of DKA have been reported with fatal outcomes. DKA can occur at any time during TRUQAP treatment. In some reported cases, DKA developed in less than 10 days.

Before initiating treatment with TRUQAP, inform patients about TRUQAP's potential to cause hyperglycaemia and request for them 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. In a setting of additional co-morbidities and treatments (e.g. dehydration, malnourishment, concurrent chemotherapy/steroids, sepsis) the risk of hyperglycaemia

progressing to diabetic ketoacidosis may be higher. DKA should be considered as one of the differential diagnoses in the event of additional non specific symptoms such as nausea, vomiting, abdominal pain, difficulty breathing, fruity odour on breath, confusion, unusual fatigue, or sleepiness. In patients where DKA is suspected, TRUQAP treatment should be interrupted immediately. If DKA is confirmed, then TRUQAP should be permanently discontinued.

Patients must be tested for fasting blood glucose (FG) levels and HbA1C prior to start of treatment with TRUQAP and in accordance with the intervals stated in Table 7. Based on the severity of hyperglycaemia, TRUQAP dosing may be interrupted, reduced, or permanently discontinued (see section 4.2, Table 3).

More frequent blood glucose monitoring is recommended in patients that develop hyperglycaemia during treatment, those with baseline risk factors for DKA (including but not exclusive to diabetes mellitus, pre-diabetes, those receiving regular oral steroids) and in those that develop risk factors for DKA during treatment (e.g., infection, sepsis, raised HbA1c) (see Table 7). In addition to FG, monitoring of ketones (preferably in blood) and other metabolic parameters (as indicated) is recommended when a patient experiences hyperglycaemia.

In addition to the recommended management of hyperglycaemia described in Section 4.2 Table 3, counselling on lifestyle changes is recommended for patients with baseline risk factors and those that develop hyperglycaemia during treatment with TRUQAP.

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 the clinical study. Patients with history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Table 7 Schedule of monitoring of fasting glucose and HbA1c levels in patients treated with TRUQAP

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with TRUQAP	**Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes and treated with TRUQAP[1]**
At screening, before initiating treatment with TRUQAP	Test for fasting glucose (FG) levels and HbA1c. Optimise the patient's level of blood glucose (see section 4.2 Table 3).	
After initiating treatment with TRUQAP	Monitor fasting glucose at weeks 1, 2, 4, 6 and 8 after start of the treatment and monthly thereafter. It is recommended to test FG pre-dose on Day 3 or 4 of the dosing week. HbA1c should be monitored every 3 months.	
	Additional monitoring/self-monitoring may be required in accordance with the instructions of a healthcare professional.	Consider monitoring/self-monitoring fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as

		frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional.[a] Additional HbA1c testing is recommended on week 4 with diabetes, pre-diabetes, or hyperglycaemia at baseline.
		Additional HbA1c testing is recommended on week 4 with diabetes, pre-diabetes, or hyperglycaemia at baseline.
If hyperglycaemia develops after initiating treatment with TRUQAP	Based on the severity of hyperglycaemia, TRUQAP dosing may be interrupted, reduced, or permanently discontinued (see section 4.2, Table 3). Monitor fasting glucose at least twice weekly, on days on and off capivasertib treatment until FG decreases to baseline levels.[a]	

	Consultation with a healthcare practitioner with expertise in the treatment of hyperglycaemia should be considered.
	During treatment with anti-diabetic medication, FG should be monitored at least once a week for 2 months, followed by once every 2 weeks or as clinically indicated.[a]
[a] It is recommended to test FG pre-dose on Day 3 or 4 of the dosing week.	

Diarrhoea

Diarrhoea has been frequently reported in patients treated with TRUQAP (see section 4.8). Based on the severity of diarrhoea, TRUQAP dosing may be interrupted, reduced, or permanently discontinued (see section 4.2, Table 4). Advise patients to start anti-diarrheal treatment at the first sign of diarrhoea, increase oral fluids if diarrhoea symptoms occur while taking TRUQAP. Maintenance of normovolaemia 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 (see section 4.8). Patients should be monitored for signs and symptoms of rash or dermatitis and based on severity of skin reactions the dosing may be interrupted, reduced, or permanently discontinued (see section 4.2, Table 5). Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

4.5 Interaction with other medicines and other forms of interaction

Effect of Other medicines on TRUQAP

Strong CYP3A4 inhibitors

Strong inhibitors increase the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) ≥ 5-fold. Concomitant use with a strong CYP3A4 inhibitor increases capivasertib concentration, which may increase the risk of TRUQAP toxicities. Reduce the dose of TRUQAP (see section 4.2). Examples of strong CYP3A4 inhibitor include, but are not limited to Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, ritonavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole. Intake of high doses of grapefruit should be avoided.

Strong CYP3A4 inducers

Strong inducers decrease the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) by ≥ 80 %. Concomitant use with a strong CYP3A4 inducer decreases capivasertib concentration which may reduce the efficacy of

TRUQAP (see section 5.2). Concomitant use of strong CYP3A4 inducers is not recommended. Examples of strong CYP3A4 inducers include Carbamazepine, phenytoin, rifampicin, St. John's wort.

Moderate CYP3A4 inducers

Moderate inducers decrease the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) by ≥ 50 % to < 80 %. There is a potential for decreased capivasertib concentration when TRUQAP concomitantly used with moderate CYP3A4 inducers. This may reduce the efficacy of TRUQAP. Moderate CYP3A4 inducers should be used with caution with TRUQAP. Examples of moderate CYP3A4 inducers include Bosentan,

cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, modafinil, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine.

Effect of TRUQAP on Other Medicines

Substrates of CYP3A

Concentration of medicines that are primarily eliminated via CYP3A metabolism may be increased by concomitant use with TRUQAP. This may result in increased toxicity of these medicines, depending on their therapeutic window. Dose adjustment may be required for medicines that are primarily eliminated via CYP3A metabolism and have a narrow therapeutic window. Refer to specific guidance in the Professional information for these medicines. Examples of Substrates of CYP3A include Carbamazepine, cyclosporine, fentanyl, pimozide, simvastatin, tacrolimus.

Hepatic transporters (OATP1B1, OATP1B3)

The concentration of medicines that are sensitive to inhibition of OATP1B1 and/or OATP1B3 if they are metabolised by CYP3A4, may increase by concomitant use with TRUQAP. This may result in increased Toxicity. Depending on their therapeutic window, dose adjustment may be required for medicines that are sensitive to inhibition of OATP1B1 and/or OATP1B3, if they are metabolised by CYP3A4. Refer to specific guidance in the Professional information for these medicines. Examples of hepatic transporters include Simvastatin.

Renal transporters (MATE1, MATE2K, OCT2)

The concentration of medicines that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by concomitant use with TRUQAP. 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. Depending on

their therapeutic window, dose adjustment may be needed for medicines that are sensitive to inhibition of MATE1, MATE2K, OCT2. Refer to specific guidance in the Professional information for these medicines. Examples of renal transporters include dofetilide and procainamide.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential/Contraception in males and females

Women of childbearing potential should not fall pregnant while receiving TRUQAP. A pregnancy test should be performed on 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.

Pregnancy

TRUQAP is not recommended during pregnancy and in women of childbearing potential not using contraception.

There are no data from the use of TRUQAP in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breastfeeding

Breastfeeding should be discontinued during treatment with TRUQAP. 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 (see section 5.3).

Fertility

There are no clinical data on fertility. In animal studies, capivasertib resulted in tubular degeneration in male reproductive organs in mice, rats and dogs but had no effects on fertility in male rats. The effect on female fertility in rats has not been studied (see section 5.3).

Please refer to section 4.6 of the Professional information for fulvestrant.

4.7 Effects on ability to drive and use machines

TRUQAP has no influence on the ability to drive and use machines. However, during treatment with TRUQAP, fatigue has been reported and those patients who experience this symptom should be advised to observe caution when driving or operating machinery.

4.8 Undesirable effects

Summary of safety profile

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 ≥ 2 %) 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 ≥ 2 %) leading to treatment discontinuation were rash (4,5 %), diarrhoea (2,0 %), and vomiting (2,0 %).

Tabulated summary of adverse 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 reactions

MedDRA SOC	**MedDRA Term**	**Any Grade (%)**	**Grade 3 or 4 (%)**
Infections and infestations	Urinary Tract Infection[1]	Very Common 48 (13,5)	6 (1,7)
Blood and lymphatic system disorders	Anaemia	Very Common 37 (10,4)	7 (2,0)
Immune system disorders	Hypersensitivity[2]	Uncommon 3 (0,8)	0
Metabolism and nutrition disorders	Hyperglycaemia[3]	Very Common 60 (16,9)	8 (2,3)
	Decreased appetite	Very Common 59 (16,6)	1 (0,3)

	Diabetic Ketoacidosis[4]	Uncommon 1 (0,3)	1 (0,3)
Nervous system disorders	Dysgeusia	Common 21 (5,9)	0
Gastrointestinal disorders	Diarrhoea[5]	Very Common 257 (72,4)	33 (9,3)
	Nausea	Very Common 123 (34,6)	3 (0,8)
	Vomiting	Very Common 73 (20,6)	6 (1,7)
	Stomatitis[6]	Very Common 61 (17,2)	7 (2,0)
	Dyspepsia	Common 18 (5,1)	0
Skin and subcutaneous tissue disorders	Rash[7]	Very Common 143 (40,3)	44 (12,4)
	Pruritis	Very Common 44 (12,4)	2 (0,6)
	Dry skin	Common 25 (7,0)	0
	Erythema multiforme	Common 6 (1,7)	3 (0,8)
	Drug Eruption	Common 4 (1,1)	4 (1,1)
	Dermatitis	Uncommon 3 (0,8)	0

	Dermatitis exfoliative generalised	Uncommon 2 (0,6)	2 (0,6)
	Toxic Skin Eruption	Uncommon 1 (0,3)	0
General disorders and administration site conditions	Fatigue	Very Common 74 (20,8)	2 (0,6)
	Mucosal inflammation	Common 11 (3,1)	1 (0,3)
Investigations	Blood creatinine increased	Common 16 (4,5)	1 (0,3)
	Glycosylated haemoglobin increased	Common 5 (1,4)	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] Diabetic Ketoacidosis includes ketoacidosis.

[5] Diarrhoea includes diarrhoea and frequent bowel movements.

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

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

Description of selected adverse reactions-

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).

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, antidiarrheal 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 TRUQAP. Dose reduction was required in 16 (4,5 %) patients and 16 (4,5 %) patients discontinued TRUQAP due to rash.

Paediatric population

Safety and efficacy of TRUQAP in children and adolescents have not been established (see section 4.2).

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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.

In overdose, side effects can be precipitated and/or be increased in severity (see section 4.8). Health care providers should follow general supportive measures and patients should be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, AKT inhibitors,

ATC code: Other protein kinase inhibitors: L01EX27

Mechanism of action

Capivasertib is a potent, selective 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 downstream 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 estrogen receptor positive (ER+) and triple negative breast cancer models with PIK3CA, AKT1 mutations, PTEN loss and HER2 amplification. 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 analysis of data from 180 patients with advanced solid malignancies who received capivasertib doses from 80 to 800 mg, the predicted QTcF prolongation was 3.87 ms at the mean steady state Cmax following 400 mg twice daily. 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.

Clinical efficacy and safety

CAPItello-291

CAPItello-291 was a randomized, double-blind, placebo-controlled study designed to demonstrate the efficacy and safety of TRUQAP in combination with fulvestrant in adult females, pre- or postmenopausal, 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.

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 randomized 1:1 to receive either 400 mg of capivasertib (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. Randomization 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 randomization 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 Tumours (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 capivasertib plus fulvestrant compared to patients receiving placebo plus fulvestrant, in both the overall population and the PIK3CA/AKT1/PTEN-altered subgroup. PFS results by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. 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 capivasertib 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.

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

Table 10: Progression-free Survival, by Investigator Assessment in Overall population and PIK3CA/AKT1/PTEN altered subgroup.

	Overall population N = 708		**PIK3CA/AKT1/PTEN altered subgroup. N = 289**	
	CAPIVASERTIB plus fulvestrant N = 355	**Placebo plus fulvestrant N = 353**	**CAPIVASERTIB plus fulvestrant N = 155**	**Placebo plus fulvestrant N = 134**
Number of PFS events – n (%)	258 (72,7)	293 (83,0)	121 (78,1)	115 (85,8)
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)
Hazard ratio (95 % CI)[a]	0,60 (0,51, 0,71)		0,50 (0,38, 0,65)	
p-value[b]	< 0,001		< 0,001	

[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)

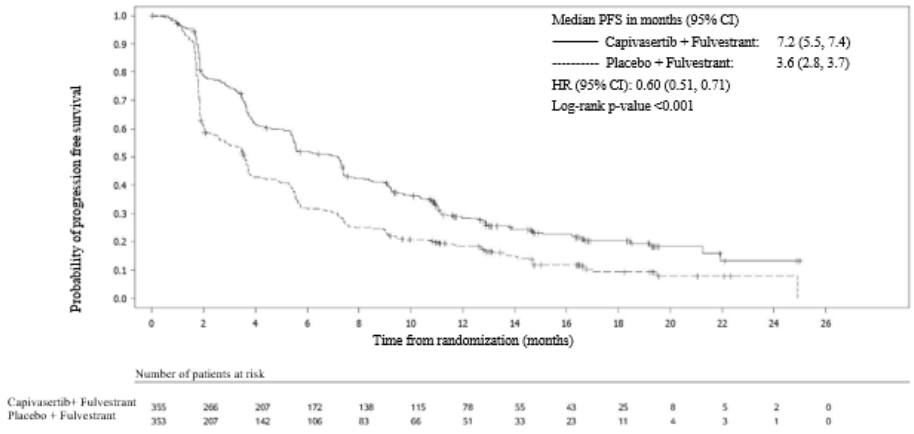
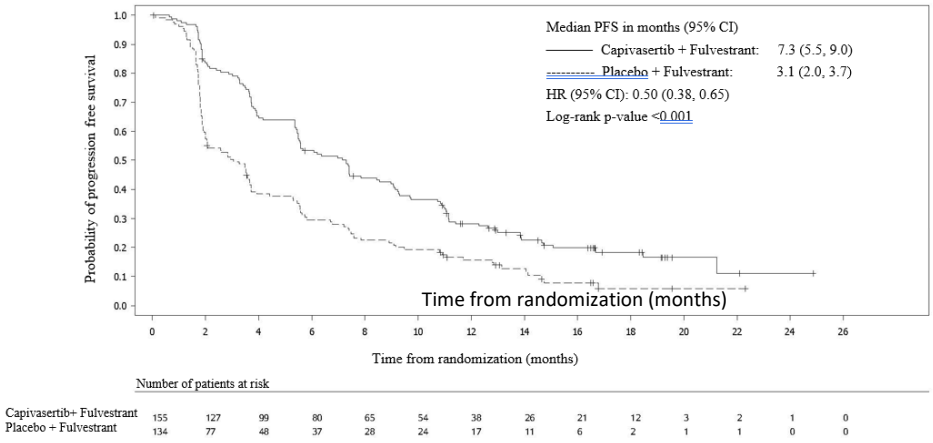


Figure 2 – Kaplan-Meier Plot of Progression-Free Survival in CAPItello-291 (Investigator Assessment, PIK3CA/AKT1/PTEN-altered subgroup)



Improvement in PFS for patients treated with capivasertib plus fulvestrant was observed across all pre-specified subgroups, including prior exposure to CDK4/6 inhibitors and in the non-altered tumour population which comprised patients with confirmed non-altered tumour population and those with no testing result available.

5.2 Pharmacokinetic properties

Capivasertib pharmacokinetics have been characterized in healthy subjects and patients with solid tumours. The systemic exposure (AUC and Cmax) 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 Cmax).

Absorption

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

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 Cmax, 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 Cmax, respectively. Co-administration with food did not result in clinically relevant changes to the exposure.

Distribution

The mean volume of distribution (Vss) 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.

Biotransformation

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.

Elimination

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.

Special populations

Effect of ethnicity, age, gender and weight

There were no clinically significant differences in pharmacokinetics of capivasertib based on 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 Cmax were 1 % higher in patients with mild renal impairment (creatinine clearance 51 to 80 mL/min), compared to patients with normal renal function. AUC and Cmax were 16 % higher in patients with moderate renal impairment (creatinine

clearance 31 to 50 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 Cmax 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 Cmax 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.

Drug-Drug Interaction

Effects of Other Medicinal Products on capivasertib

In vitro studies have demonstrated that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes.

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.

Effects of capivasertib on Other Medicinal Products

Co-administration of capivasertib 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 metabolizing enzymes and BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K drug transporters in *in vitro* studies.

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. No meaningful interaction was predicted for metformin (2 % to 40 % AUC increase, depending on the capivasertib dosing day).

5.3 Preclinical safety data

The major target organs or systems for toxicity were insulin signalling (increased levels glucose and insulin in rats and dogs), the male reproductive organs (tubular degeneratic in in rats and dogs), and the renal system in rats (polyuria, decreased tubular epitheli 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).

Capivasertib showed no mutagenic or genotoxic potential in vitro. When dosed orally to rats, capivasertib induced micronuclei in the bone marrow via an aneugenic mode of action.

Carcinogenicity studies have not been conducted with capivasertib.

Embryofetal/Developmental 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. 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.

Exposure to capivasertib was confirmed in suckling pups which may indicate the potential for excretion of capivasertib in human milk (see section 4.6).

Capivasertib had no effect on fertility in male rats. Effects on female fertility have not been studied in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Dibasic calcium phosphate

Croscarmellose sodium

Magnesium stearate

Tablet coating:

Hypromellose

Titanium dioxide

Polyethylene glycol 3350

Polydextrose

Copovidone

Medium chain triglycerides

Yellow iron oxide

Red iron oxide

Black iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in original package at or below 30 ºC.

Avoid excursions above 30 ºC.

6.5 Nature and contents of container

TRUQAP tablets 160 mg and 200 mg

Aluminium/Aluminium blister containing 16 film-coated tablets. Pack of 64 tablets (4 blisters).

Pack size of 64 tablets.

6.6 Special precautions for disposal and handling

TRUQAP: Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

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17 Georgian Crescent West, Bryanston

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8 REGISTRATION NUMBERS

61/26/0291

61/26/0292

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 February 2026

10 DATE OF REVISION OF THE TEXT

Not applicable