Prescriber guide

This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

1 NAME OF THE MEDICINAL PRODUCT

TRUQAP 160 mg

TRUQAP 200 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

TRUQAP 160 mg:

Capivasertib 160 mg, film-coated tablets

TRUQAP 200 mg:

Capivasertib 200 mg, film-coated tablets

2 THERAPEUTIC INDICATIONS

TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

3 DOSAGE AND ADMINISTRATION

3.1 Patient Selection

Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with TRUQAP, based on the presence of one or more of the following genetic alterations in tumor tissue: PIK3CA/AKT1/PTEN [see Clinical Studies (13)].

3.2 Recommended Evaluation Before Initiating TRUQAP

Evaluate fasting blood glucose (FG) and hemoglobin A1C (HbA1C) prior to starting TRUQAP and at regular intervals during treatment [see Warnings and Precautions (6)].

3.3 Recommended Dosage and Administration

The recommended dosage of TRUQAP, in combination with fulvestrant, is 400 mg orally twice daily (approximately 12 hours apart) with or without food, for 4 days followed by 3 days off. Continue TRUQAP until disease progression or unacceptable toxicity. TRUQAP dosing schedule for each week is provided in Table 1.

Table 1: TRUQAP Dosing Schedule for Each Week

Day	1	2	3	4	5*	6*	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.

Swallow TRUQAP tablets whole. Do not chew, crush, or split tablets prior to swallowing. Do not take tablets that are broken, cracked, or otherwise not intact.

If a patient misses a dose within 4 hours of the scheduled time, instruct the patient to take the missed dose.

If a patient misses a dose more than 4 hours of the scheduled time, instruct the patient to skip the dose and take the next dose at its usual scheduled time.

If a patient vomits a dose, instruct the patient not to take an additional dose and take the next dose at its usual scheduled time.

Refer to the fulvestrant Full Prescribing Information for recommended fulvestrant dosing information.

For premenopausal and perimenopausal women, administer a luteinizing hormone-releasing hormone (LHRH) agonist according to current clinical practice standards.

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

3.4 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are listed in Table 2.

Permanently discontinue TRUQAP if unable to tolerate the second dose reduction.

Table 2. Recommended Dose Reductions of TRUQAP for Adverse Reactions

TRUQAP	**Dose and Schedule**
First dose reduction	320 mg twice daily for 4 days followed by 3 days off
Second dose reduction	200 mg twice daily for 4 days followed by 3 days off

The recommended dosage modifications for adverse reactions are provided in Table 3.

Table 3: Recommended Dosage Modifications of TRUQAP for Adverse Reactions

Adverse Reaction	**Severity***	**TRUQAP Dosage Modification**
Hyperglycemia (Fasting Glucose [FG]) [see Warnings and Precautions (6.1)]	FG > ULN-160 mg/dL or FG > ULN-8.9 mmol/L or HbA1C > 7%	Consider initiation or intensification of oral antidiabetic treatment.
	FG 161-250 mg/dL or FG 9-13.9 mmol/L	Withhold TRUQAP until FG decrease ≤ 160 mg/dL (or ≤ 8.9 mmol/L) If recovery occurs in ≤ 28 days, resume TRUQAP at same dose. If recovery occurs in > 28 days, resume TRUQAP at one lower dose.
	FG 251-500 mg/dL or FG 14-27.8 mmol/L	Withhold TRUQAP until FG decrease ≤ 160 mg/dL (or ≤ 8.9 mmol/L) If recovery occurs in ≤ 28 days, resume TRUQAP at one lower dose. If recovery occurs in > 28 days, permanently. discontinue TRUQAP.

Adverse Reaction	Severity*	TRUQAP Dosage Modification
	FG > 500 mg/dL or FG > 27.8 mmol/L or life-threatening sequelae of hyperglycemia at any FG level	For life-threatening sequelae of hyperglycemia or if FG persists at ≥ 500 mg/dL after 24 hours, permanently discontinue TRUQAP. If FG ≤ 500 mg/dL (or ≤ 27.8 mmol/L) within 24 hours, then follow the guidance in the table for the relevant grade.
Diarrhea [see Warnings and Precautions (6.2)]	Grade 2	Withhold TRUQAP until recovery to ≤ grade 1 If recovery occur in ≤ 28 days, resume TRUQAP at same dose or one lower dose as clinically indicated. If recovery occurs in > 28 days, resume at one lower dose as clinically indicated. For recurrence, reduce TRUQAP by one lower dose.
	Grade 3	Withhold TRUQAP until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume TRUQAP at same dose or one lower dose as clinically indicated. If recovery occurs in > 28 days, permanently discontinue TRUQAP.
	Grade 4	Permanently discontinue TRUQAP
Cutaneous Adverse Reactions [see Warnings and Precautions (6.3)]	Grade 2	Withhold TRUQAP until recovery to ≤ Grade 1. Resume TRUQAP at the same dose. Persistent or recurrent: reduce TRUQAP by one lower dose.
	Grade 3	Withhold TRUQAP until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume TRUQAP at same dose. If recovery occurs in > 28 days, resume TRUQAP at one lower dose. For recurrent Grade 3, permanently discontinue TRUQAP.
	Grade 4	Permanently discontinue TRUQAP

Adverse Reaction	Severity*	TRUQAP Dosage Modification
Other Adverse Reactions [see Adverse Reactions (7.1)]	Grade 2	Withhold TRUQAP until recovery to ≤ Grade 1. Resume TRUQAP at the same dose.
	Grade 3	Withhold TRUQAP until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume TRUQAP at same dose. If recovery occurs in > 28 days, resume TRUQAP at one lower dose.
	Grade 4	Permanently discontinue TRUQAP

*Severity grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

3.5 Dosage Modifications for Strong and Moderate CYP3A Inhibitors

Avoid concomitant use with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the dosage of TRUQAP to 320 mg orally twice daily for 4 days followed by 3 days off [see Drug Interactions (8.1)].

When concomitantly used with a moderate CYP3A inhibitor, reduce the dosage of TRUQAP to 320 mg orally twice daily for 4 days followed by 3 days off. After discontinuation of a strong or moderate CYP3A inhibitor, resume the TRUQAP dosage (after 3 to 5 half-lives of the inhibitor) that was taken prior to initiating the strong or moderate CYP3A inhibitor.

4 DOSAGE FORMS AND STRENGTHS

- TRUQAP 160 mg: beige film-coated, round, biconvex tablets debossed with ‘CAV’ above ‘160’ on one side and plain on the reverse.
- TRUQAP 200 mg: beige film-coated, capsule-shaped, biconvex tablets debossed with ‘CAV 200’ on one side and plain on the reverse.

5 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 10.

6 WARNINGS AND PRECAUTIONS

6.1 Hyperglycemia

Severe hyperglycemia, associated with ketoacidosis, occurred in patients treated with TRUQAP. The safety of TRUQAP has not been established in patients with Type I diabetes or diabetes requiring insulin. Patients with insulin dependent diabetes were excluded from CAPItello-291.

Hyperglycemia occurred in 18% of patients treated with TRUQAP. Grade 3 (insulin therapy initiated; hospitalization indicated) or Grade 4 (life-threatening consequences; urgent intervention indicated) hyperglycemia occurred in 2.8% of patients. Diabetic ketoacidosis occurred in 0.3% of patients and diabetic metabolic decompensation in 0.6% of patients. Dose reduction for hyperglycemia was required in 0.6% of patients and permanent discontinuation was required in 0.6% of patients. The median time to first occurrence of hyperglycemia was 15 days (range: 1 to 367).

In the 65 patients with hyperglycemia, 45% required treatment with anti-hyperglycemic medication (insulin in 15%, and metformin in 29%). Of the 29 patients who required anti-hyperglycemic medication during treatment with TRUQAP, 66% (19/29) remained on these medications at treatment discontinuation or last follow up.

Evaluate fasting blood glucose (FG) and hemoglobin A1C (HbA1c) and optimize blood glucose prior to treatment. Before initiating TRUQAP, inform patients about TRUQAP's potential to cause hyperglycemia and to immediately contact their healthcare professional if hyperglycemia symptoms occur (e.g., excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss). Evaluate FG at least every two weeks during the first month and at least once a month starting from the second month, prior to the scheduled dose of TRUQAP. Monitor HbA1c every three months. Monitor FG

more frequently during treatment with TRUQAP in patients with a medical history of diabetes mellitus and in patients with risk factors for hyperglycemia such as obesity (BMI ≥ 30), elevated FG of > 160 mg/dL (> 8.9 mmol/L), HbA1c at or above the upper limit of normal, use of concomitant systemic corticosteroids, or intercurrent infections.

If a patient experiences hyperglycemia after initiating treatment with TRUQAP, monitor FG as clinically indicated, and at least twice weekly until FG decreases to normal levels. During treatment with anti- hyperglycemic medication, continue monitoring FG at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a healthcare practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes. Withhold, reduce dose, or permanently discontinue TRUQAP based on severity [see Dosage and Administration (3.4)].

6.2 Diarrhea

Severe diarrhea associated with dehydration occurred in patients who received TRUQAP. Diarrhea occurred in 72% of patients. Grade 3 or 4 diarrhea occurred in 9% of patients. The median time to first occurrence was 8 days (range 1 to 519). In the 257 patients with diarrhea, 59% required anti-diarrheal medications to manage symptoms. Dose reductions were required in 8% of patients, and 2% of patients permanently discontinued TRUQAP due to diarrhea. In patients with Grade ≥ 2 diarrhea (n=93) with at least 1 grade improvement (n=89), median time to improvement from the first event was 4 days (range: 1 to 154).

Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start antidiarrheal treatment at the first sign of diarrhea while taking TRUQAP. Withhold, reduce dose, or permanently discontinue TRUQAP based on severity [see Dosage and Administration (3.4)].

6.3 Cutaneous Adverse Reactions

Cutaneous adverse reactions, which can be severe, including erythema

multiforme (EM), palmar-plantar erythrodysesthesia, and drug reaction with eosinophilia and systemic symptoms (DRESS), occurred in patients who received TRUQAP.

Cutaneous adverse reactions occurred in 58% of patients. Grade 3 or 4 cutaneous adverse reactions occurred in 17% of patients receiving TRUQAP. EM occurred in 1.7% of patients and DRESS occurred in 0.3% of patients. Dose reduction was required in 7% of patients and 7% of patients permanently discontinued TRUQAP due to cutaneous adverse reactions.

The median time to onset of cutaneous adverse reactions was 13 days (range 1 to 575 days). Among the 204 patients with cutaneous adverse reactions, 44% (90/204) required corticosteroid treatment. Of these, 37% (76/204) were treated with topical corticosteroids and 19% (39/204) with systemic corticosteroids. In patients with Grade ≥ 2 cutaneous adverse reaction (n= 116) with at least 1 grade improvement (n=104), median time to improvement from the first event was 12 days (range 2 to 544).

Monitor patients for signs and symptoms of cutaneous adverse reactions. Early consultation with a dermatologist is recommended. Withhold, reduce dose, or permanently discontinue TRUQAP based on severity [see Dosage and Administration (3.4)].

6.4 Embryo-Fetal Toxicity

Based on findings from animals and mechanism of action, TRUQAP can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (11.1)]. In an animal reproduction study, oral administration of capivasertib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, and reduced fetal weights at maternal exposures 0.7 times the human exposure (AUC) at the recommended dosage of 400 mg twice daily.

Advise pregnant women and females of reproductive potential of the potential

risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRUQAP and for 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRUQAP and for 4 months after the last dose [see Use in Specific Populations (9.1, 9.3)].

TRUQAP is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for pregnancy and contraception information.

7 ADVERSE REACTIONS

The following adverse reactions are also discussed in greater details in other sections of the labeling:

- Hyperglycemia [see Warnings and Precautions (6.1)]
- Diarrhea [see Warnings and Precautions (6.2)]
- Cutaneous Adverse Reactions [see Warnings and Precautions (6.3)]

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in WARNINGS and PRECAUTIONS reflects exposure to TRUQAP 400 mg orally, twice a day for 4 days followed by 3 days off, in combination with fulvestrant, in 355 patients in CAPItello-291 until disease progression or unacceptable toxicity. Among the 355 patients who received TRUQAP, 52% were exposed for 6 months or longer, and 27% were exposed for greater than one year. In this safety population, the most common (≥20%) adverse reactions including laboratory abnormalities were diarrhea (72%), cutaneous adverse reactions (58%), increased random glucose (57%), decreased lymphocytes (47%), decreased hemoglobin (45%), increased fasting

glucose (37%), nausea and fatigue (35% each), decreased leukocytes (32%), increased triglycerides (27%), decreased neutrophils (23%), increased creatinine (22%), vomiting (21%), and stomatitis (20%).

CAPItello-291

The safety of TRUQAP was evaluated in CAPItello-291, a clinical trial including 288 adult patients (155 patients in TRUQAP with fulvestrant arm and 133 patients in placebo with fulvestrant arm) whose breast cancer had one or more PIK3CA/AKT1/PTEN-alterations [see Clinical Studies (13)]. Among patients who received TRUQAP, 61% were exposed for 6 months or longer and 30% were exposed for greater than one year.

Of the 155 patients who received TRUQAP with fulvestrant, the median age was 58 years (range 36 to 84); female (99%); White (48%), Asian (31%), Black (1.3%), American Indian/Alaska Native (0.6%), and other races (19%).
Serious adverse reactions occurred in 18% of patients receiving TRUQAP with fulvestrant. The most common serious adverse reactions (≥1%) were cutaneous adverse reaction (3.9%), diarrhea and pneumonia (2.6% each), vomiting and pyrexia (1.9% each), hyperglycemia, hypersensitivity, fatigue, renal injury and second malignancy (1.3% each).
Fatal adverse reactions occurred in 1.3% of patients who received TRUQAP with fulvestrant, including sepsis (0.6%), and acute myocardial infarction (0.6%).

Permanent TRUQAP discontinuation due to an adverse reaction occurred in 10% of patients. The most common adverse reaction (≥ 2%) leading to permanent discontinuation of TRUQAP was cutaneous adverse reactions (6%). Dosage interruptions of TRUQAP due to an adverse reaction occurred in 39% of patients. Adverse reactions leading to dosage interruption in ≥ 2% of patients included cutaneous adverse reactions (14%), diarrhea (10%), pyrexia (4.5%), vomiting and nausea (3.2% each), and fatigue (2.6%).

Dose reductions of TRUQAP due to adverse reactions occurred in 21% of

patients receiving TRUQAP with fulvestrant. Adverse reactions leading to TRUQAP dose reductions in ≥ 2% of patients were diarrhea and cutaneous adverse reactions (8% each).

The most common (≥ 20%) adverse reactions including laboratory abnormalities were diarrhea (77%), increased random glucose (58%), cutaneous adverse reaction (56%), decreased lymphocytes (49%) decreased hemoglobin (47%), fatigue (38%), increased fasting glucose (37%), nausea and decreased leukocytes (35% each), increased triglycerides (30%), stomatitis (25%), decreased neutrophils (25%), and vomiting (21%). Adverse reactions and laboratory abnormalities are listed in Table 4 and Table 5, respectively.

Table 4. Adverse Reactions ≥ 10% in patients who Received TRUQAP with Fulvestrant [with a Difference Between Arms of ≥ 3%] in CAPItello-291

Adverse Reaction	TRUQAP with Fulvestrant N=155		Placebo with Fulvestrant N=133	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Gastrointestinal Disorders				
Diarrhea	77	12	19	0.8
Nausea	35	1.3	14	0.8
Stomatitis*	25	1.9	5	0
Vomiting	21	1.9	7	0.8
Skin and Subcutaneous Tissue Disorders				
Cutaneous adverse reactions†	56	15	16	0.8
General Disorders and Administration Site Conditions				
Fatigue*	38	1.9	27	1.5
Metabolism and Nutrition Disorders				
Hyperglycemia‡	19	1.9	4.5	0
Decreased appetite	17	0	8	0.8
Nervous System Disorders				
Headache*	17	0	13	0.8
Infections and Infestations				
Urinary tract infection*	14	0.6	5	0

Renal and Urinary disorders				
Renal injury§	11	2.6	1.5	0.8

* Includes other related terms.

†Cutaneous adverse reaction includes butterfly rash, dermatitis, allergic dermatitis, dry skin, eczema, erythema multiforme, hand dermatitis, palmar-plantar erythrodysesthesia syndrome, pruritus, rash, erythematous rash, maculo-papular rash, papular rash, skin discoloration, skin fissures, skin reaction, skin ulcer, urticaria, purpura, erythema and drug eruption.

‡ Hyperglycemia includes hyperglycemia, blood glucose increased, glycosylated hemoglobin increased, glucose tolerance impaired and diabetes mellitus.

§ Renal injury includes acute kidney injury, renal failure, renal impairment, glomerular filtration rate decreased, increased creatinine and proteinuria.

Clinically relevant adverse reactions occurring in < 10% of patients treated with TRUQAP included anemia, hypersensitivity (including anaphylactic reaction), dysgeusia, dyspepsia, pneumonia and pyrexia.

Table 5: Laboratory Abnormalities (> 10%) in patients who Received TRUQAP with Fulvestrant [With a Difference Between Arms >3%] in CAPItello-291

Laboratory Abnormality	TRUQAP with Fulvestrant*		Placebo with Fulvestrant†	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Glucose Metabolism				
Increased random glucose	58	9	17	0
Increased fasting glucose	37	0.6	29	0
Hematology				
Decreased lymphocytes	49	11	14	2.3
Decreased hemoglobin	47	2	22	2.3
Decreased leukocytes	35	0.6	23	0
Decreased neutrophils	25	1.9	16	0.8
Decreased platelets	12	1.9	6	0.8
Other Categories				
Increased triglycerides	30	0.7	22	0.9
Increased alanine aminotransferase	23	2.6	13	0
Electrolytes/Renal				

Decreased corrected calcium	19	0.6	8	0
Increased creatinine	19	1.3	4.6	0.8
Decreased potassium	17	4.5	8	0

*The denominator used to calculate the rate varied from 129 to 155 based on the number of patients with a baseline value and at least one post-treatment value.

†The denominator used to calculate the rate varied from 109 to 131 based on the number of patients with a baseline value and at least one post-treatment value.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

8 DRUG INTERACTIONS

8.1 Effects of Other Drugs on TRUQAP

Table 6 describes drug interactions where concomitant use of another drug affects TRUQAP.

Table 6: Drug Interactions with TRUQAP

Strong CYP3A Inhibitors	
Clinical Impact	• Capivasertib is a CYP3A substrate. Strong CYP3A inhibitors increase capivasertib exposure *[see Clinical Pharmacology (11.3)]*, which may increase the risk of TRUQAP adverse reactions.
Prevention or Management	• Avoid concomitant use with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce the dose of TRUQAP and monitor patients for adverse reactions *[see Dosage and Administration (3.5)]*.

Moderate CYP3A Inhibitors	
Clinical Impact	• Capivasertib is a CYP3A substrate. Moderate CYP3A inhibitors increase capivasertib exposure *[see Clinical Pharmacology (11.3)],* which may increase the risk of TRUQAP adverse reactions.
Prevention or Management	• When concomitantly used with moderate CYP3A inhibitor, reduce the dose of TRUQAP and monitor patients for adverse reactions *[see Dosage and Administration (3.5)]*.
Strong and Moderate CYP3A Inducers	
Clinical Impact	• Capivasertib is a CYP3A substrate. Strong and moderate CYP3A inducers decrease capivasertib exposure *[see Clinical Pharmacology (11.3)],* which may reduce the effectiveness of TRUQAP.
Prevention or Management	• Avoid concomitant use of TRUQAP with strong or moderate CYP3A inducers.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

TRUQAP is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for pregnancy information.

Based on findings in animals and mechanism of action, TRUQAP can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (11.1)]. There are no available data on the use of TRUQAP in pregnant women. In an animal reproduction study, oral administration of capivasertib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality and reduced fetal weights at maternal exposures 0.7 times the human exposure (AUC) at the recommended dose of

400 mg twice daily (see Data). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of capivasertib up to 150 mg/kg/day during the period of organogenesis. Administration of capivasertib resulted in maternal toxicities (reduced body weight gain and food consumption, increased blood glucose) and adverse developmental outcomes, including embryo-fetal deaths (post-implantation loss), reduced fetal weights, and minor fetal visceral variations at a dose of 150 mg/kg/day (0.7 times the human exposure at the recommended dose of 400 mg twice daily based on AUC).

In a pre- and post-natal assessment, pregnant rats received oral doses of capivasertib up to 150 mg/kg/day from gestation day 6 through at least lactation day 6. Administration of 150 mg/kg/day resulted in reduced litter and pup weights.

9.2 Lactation

Risk Summary

TRUQAP is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for lactation information.

There are no data on the presence of capivasertib or its metabolites in human milk or their effects on milk production or the breastfed child. Capivasertib was detected in the plasma of suckling rat pups (see Data). Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TRUQAP.

Data

Animal Data

In a pre- and post-natal assessment, when capivasertib was administered to maternal rats during the lactation period, capivasertib was detected in plasma of suckling rat pups on lactation day 7 to 8 [see Use in Specific Populations (9.1)]. Plasma concentrations in pups were up to 0.6% of concentrations in maternal plasma in the 150 mg/kg/day group.

9.3 Females and Males of Reproductive Potential

TRUQAP is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for contraception and infertility information. TRUQAP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (9.1)].

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating TRUQAP [see Use in Specific Populations (9.1)].

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TRUQAP and for 1 month after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRUQAP and for 4 months after the last dose.

9.4 Pediatric Use

The safety and effectiveness of TRUQAP have not been established in pediatric patients

9.5 Geriatric Use

Of the 355 patients who received TRUQAP in CAPItello-291, 115 (32%) patients were ≥ 65 years of age and 24 (7%) patients were ≥ 75 years of age. No overall differences in the efficacy of TRUQAP were observed between patients≥ 65 years of age and younger patients. Analysis of the safety of TRUQAP comparing patients ≥ 65 years of age to younger patients suggest a higher incidence of Grade 3 to 5 adverse reactions (57% versus 36%), dosage reductions (30% versus 15%), dose interruptions (57% versus 30%), and permanent discontinuations (23% versus 8%), respectively.

9.6 Renal Impairment

No dosage modification is recommended for patients with mild to moderate (creatinine clearance (CLcr) 30 to 89 mL/min) renal impairment [see Clinical Pharmacology (11.3)].

TRUQAP has not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment.

9.7 Hepatic Impairment

No dosage modification is recommended for patients with mild hepatic impairment (bilirubin ≤ upper limit of normal (ULN) and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST) [see Clinical Pharmacology (11.3)].

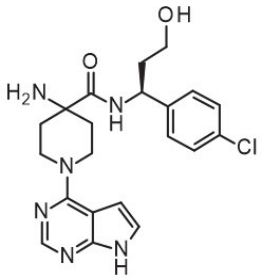
Monitor patients with moderate (bilirubin > 1.5 to 3x ULN and any AST) hepatic impairment for adverse reactions due to potential increased capivasertib exposure [see Warnings and Precautions (5.1, 5.2, 5.3)].

TRUQAP has not been studied in patients with severe (bilirubin > 3x ULN and any AST) hepatic impairment.

10 DESCRIPTION

TRUQAP (capivasertib) is a kinase inhibitor. The molecular formula for capivasertib is $C_{21}H_{25}ClN_6O_2$ and the molecular weight is 428.92 g/mol. The

chemical name of capivasertib is 4-amino-N-[(1S)-1-(4- chlorophenyl)-3-hydroxypropyl]-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidinecarboxamide. Capivasertib is a white to off-white powder with pH-dependent solubility. It is freely soluble in water at pH values below 1.2 and practically insoluble at pH values above 6.8. Capivasertib has the following structural formula:



TRUQAP film-coated tablets are supplied for oral administration with 160 mg or 200 mg capivasertib. The tablets also contain cellulose, microcrystalline, calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The film coat contains the following inactive ingredients: Hypromellose, copovidone, titanium dioxide, polydextrose, macrogols 3350, medium chain triglycerides, , iron oxide yellow, iron oxide red, iron oxide black and purified water. , , , ,

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Capivasertib is an inhibitor of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3) and inhibits phosphorylation of downstream AKT substrates. AKT activation in tumors is a result of activation of upstream signaling pathways, mutations in AKT1, loss of phosphatase and tensin homolog (PTEN) function and mutations in the catalytic subunit alpha of phosphatidylinositol 3-kinase (PIK3CA). In vitro, capivasertib reduced growth of breast cancer cell lines including those with relevant PIK3CA or AKT1 mutations or PTEN alteration. In vivo, capivasertib alone and in combination with fulvestrant inhibited tumor growth of mouse xenograft models including estrogen receptor positive breast

cancer models with alterations in PIK3CA, AKT1, and PTEN.

11.2 Pharmacodynamics

Exposure-Response Relationships

The exposure-response relationship and time course of pharmacodynamic response for the effectiveness of capivasertib have not been fully characterized. Exposure-response relationships were observed for diarrhea (CTCAE Grade 2 to 4), rash (CTCAE Grade 2 to 4) and hyperglycemia (CTCAE Grades 3 or 4) at doses of 80 to 800 mg (0.2 to 2 times the approved recommended dosage).

Cardiac Electrophysiology

At the recommended TRUQAP dose, a mean increase in the QTc interval > 20 ms was not observed.

11.3 Pharmacokinetics

Capivasertib pharmacokinetic parameters are presented as the mean [%coefficient of variation (%CV)], unless otherwise specified. The capivasertib steady-state AUC is 8,069 h·ng/mL (37%) and Cmax is 1,371 ng/mL (30%). Steady-state concentrations are predicted to be attained on the 3rd and 4th dosing day of each week, starting week 2.

Capivasertib plasma concentrations are approximately 0.5% to 15% of the steady state Cmax during the off- dosing days.

Capivasertib AUC and Cmax are proportional with dose over a range of 80 to 800 mg (0.2 to 2 times the approved recommended dosage).

Absorption

T_{max} is approximately 1-2 hours. The absolute bioavailability is 29%.

Effect of Food

No clinically meaningful differences in capivasertib pharmacokinetics were observed following administration of TRUQAP with a high-fat meal (approximately 1,000 kcal; fat 60%) or a low-fat meal (approximately 400 kcal; fat 26%).

Distribution

The steady state oral volume of distribution is 1,847 L (36%). Capivasertib plasma protein binding is 78% and the plasma-to-blood ratio is 0.71.

Elimination

The half-life is 8.3 hours and the steady-state oral clearance is 50 L/h (37% CV). Renal clearance was 21% of total clearance.

Metabolism

Capivasertib is primarily metabolized by CYP3A4 and UGT2B7.

Excretion

Following a single radiolabeled oral dose of 400 mg, the mean total recovery was 45% from urine and 50% from feces.

Specific Populations

No clinically significant differences in capivasertib pharmacokinetics were observed based on race/ethnicity (including White, Asian, Black, American Indian or Alaskan Native, and Native Hawaiian or Other Pacific Islander), sex (88% females), body weight (32 to 150 kg), age (26 to 87 years), mild hepatic impairment (bilirubin ≤ULN and AST > ULN or bilirubin > 1 to 1.5x ULN), or mild to moderate renal impairment (CLcr 30 to 89 mL/min).

The effect of moderate (bilirubin > 1.5 to 3x ULN and any AST) hepatic impairment is not fully characterized.

TRUQAP has not been studied in patients with severe (bilirubin > 3x ULN and any AST) hepatic impairment or severe renal impairment (CLcr 15 to 29 mL/min).

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Strong and Moderate CYP3A Inhibitors on Capivasertib: Itraconazole (strong CYP3A4 inhibitor) is predicted to increase capivasertib AUC by up to 1.7-fold and C_{max} by up to 1.4-fold.

Erythromycin and verapamil (moderate CYP3A inhibitors) are predicted to increase capivasertib AUC by up to 1.5-fold and C_{max} by up to 1.3-fold.

Effect of Strong and Moderate CYP3A Inducers on Capivasertib: Rifampicin (strong CYP3A4 inducer) is predicted to decrease capivasertib AUC by 70% and C_{max} by 60%.

Efavirenz (moderate CYP3A4 inducer) is predicted to decrease capivasertib AUC by 60% and C_{max} by 50%.

Effect of UGT2B7 Inhibitors on Capivasertib: Probenecid (UGT2B7 inhibitor) is not predicted to have a clinically meaningful effect on capivasertib pharmacokinetics.

Effect of Acid Reducing Agents on Capivasertib: Rabeprazole (gastric acid reducing agent) did not have a clinically meaningful effect on capivasertib pharmacokinetics.

Effect of Capivasertib on CYP3A Substrates: Concomitant use of TRUQAP increased midazolam (CYP3A substrate) AUC by 1.8-fold on day 4 and by 1.2-fold on day 7.

Effect of Capivasertib on CYP2D6 Substrates: TRUQAP is predicted to increase desipramine (CYP2D6 substrate) AUC by up to 2.1-fold on day 4.

Effect of Capivasertib on CYP2C9 Substrates: Concomitant use of TRUQAP with warfarin (CYP2C9 substrate) is not predicted to have a clinically meaningful effect on warfarin pharmacokinetics.

Effect of Capivasertib on UGT1A1 Substrates: TRUQAP is predicted to increase raltegravir (UGT1A1 substrate) AUC by up to 1.7-fold on day 4.

In-Vitro Studies

Capivasertib inhibits BCRP, OATP1B1, OATP1B3, OAT3, MATE1, MATE2-K, and OCT2.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with capivasertib.

Capivasertib was genotoxic in the in vivo rat bone marrow micronucleus assay through an aneugenic mechanism. Capivasertib was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay or mouse lymphoma gene mutation assay.

In repeat-dose toxicity studies up to 26 weeks duration in rats and 39 weeks duration in dogs, tubular degeneration in the testes and cellular debris in the epididymides were observed at oral capivasertib doses of 100 mg/kg/day in rats and 15 mg/kg/day in dogs (approximately 1 time the human exposure at the recommended dose of 400 mg twice daily based on AUC). In a male fertility study, capivasertib had no effect on fertility in male rats at oral doses up to 100 mg/kg/day following 10 weeks of treatment. Effects of capivasertib on female fertility have not been studied in animals.

13 CLINICAL STUDIES

The efficacy of TRUQAP with fulvestrant was evaluated in CAPItello-291 (NCT04305496), a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 708 adult patients with locally advanced (inoperable) or metastatic HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) breast cancer of which 289 patients had tumors with eligible PIK3CA/AKT1/PTEN-alterations. Eligible PIK3CA/AKT1 activating mutations or PTEN loss of function alterations were identified in the majority of FFPE tumor specimens using FoundationOne®CDx next-generation sequencing (n=686). All patients were required to have progression on an aromatase inhibitor (AI) based treatment in the metastatic setting or recurrence on or within 12 months of completing (neo)adjuvant treatment with an AI. Patients could have received up to two prior

lines of endocrine therapy and up to 1 line of chemotherapy for locally advanced (inoperable) or metastatic disease. Patients were excluded if they had clinically significant abnormalities of glucose metabolism (defined as patients with diabetes mellitus Type 1, Type 2, requiring insulin treatment, or HbA1c ≥ 8% (63.9 mmol/mol)).

Patients were randomized (1:1) to receive either 400 mg of TRUQAP (n=355) or placebo (n=353), given orally twice daily for 4 days followed by 3 days off treatment each week of 28-day treatment cycle. Fulvestrant 500 mg intramuscular injection was administered on cycle 1 days 1 and 15, and then at day 1 of each subsequent 28-day cycle. Patients were treated until disease progression, or unacceptable toxicity. Randomization was stratified by presence of liver metastases (yes vs. no), prior treatment with CDK4/6 inhibitors (yes vs. no) 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).

The major efficacy outcomes were investigator-assessed progression-free survival (PFS) in the overall population, and in the population of patients whose tumors have PIK3CA/AKT1/PTEN-alterations evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Additional efficacy outcome measures were overall survival (OS), investigator assessed objective response rate (ORR) and duration of response (DoR).

A statistically significant difference in PFS was observed in the overall population and the population of patients whose tumors have PIK3CA/AKT1/PTEN-alteration. An exploratory analysis of PFS in the 313 (44%) patients whose tumors did not have a PIK3CA/AKT1/PTEN-alteration showed a HR of 0.79 (95% CI: 0.61, 1.02), indicating that the difference in the overall population was primarily attributed to the results seen in the population of patients whose tumors

have PIK3CA/AKT1/PTEN-alteration.

Of the 289 patients whose tumors were PIK3CA/AKT1/PTEN-altered, the median age was 59 years (range 34 to 90); female (99%); White (52%), Asian (29%), Black (1%), American Indian/Alaska Native (0.7%), other races (17%) and 9% were Hispanic/Latino. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (66%) or 1 (34%), and 18% were premenopausal or perimenopausal. Seventy-six percent of patients had an alteration in PIK3CA, 13% had an alteration in AKT1, and 17% had an alteration in PTEN. All patients received prior endocrine-based therapy (100% AI based treatment and 44% received tamoxifen). Seventy-one percent of patients were previously treated with a CDK4/6 inhibitor and 18% received prior chemotherapy for locally advanced (inoperable) or metastatic disease.

Efficacy results for PIK3CA/AKT1/PTEN-altered subgroup are presented in Table 7 and Figure 1. Results from the blinded independent review committee (BICR) assessment were consistent with the investigator assessed PFS results. Overall survival results were immature at the time of the PFS analysis (30% of the patients died).

Table 7: Efficacy Results for CAPItello-291 (Patients with PIK3CA/AKT1/PTEN-Altered Tumors)

	TRUQAP with fulvestrant N=155	**Placebo with fulvestrant N=134**
Investigator-Assessed Progression-Free Survival (PFS)		
Number of events (%)	121 (78%)	115 (86%)
Median, months (95%CI)	7.3 (5.5, 9.0)	3.1 (2.0, 3.7)
Hazard ratio (95% CI) *	0.50 (0.38, 0.65)	
p-value†	<0.0001	
Investigator-Assessed Confirmed Objective Response Rate (ORR)		
Patients with measurable disease	132	124
ORR (95% CI)	26% (19,34)	8% (4,14)
Complete response rate	2.3%	0

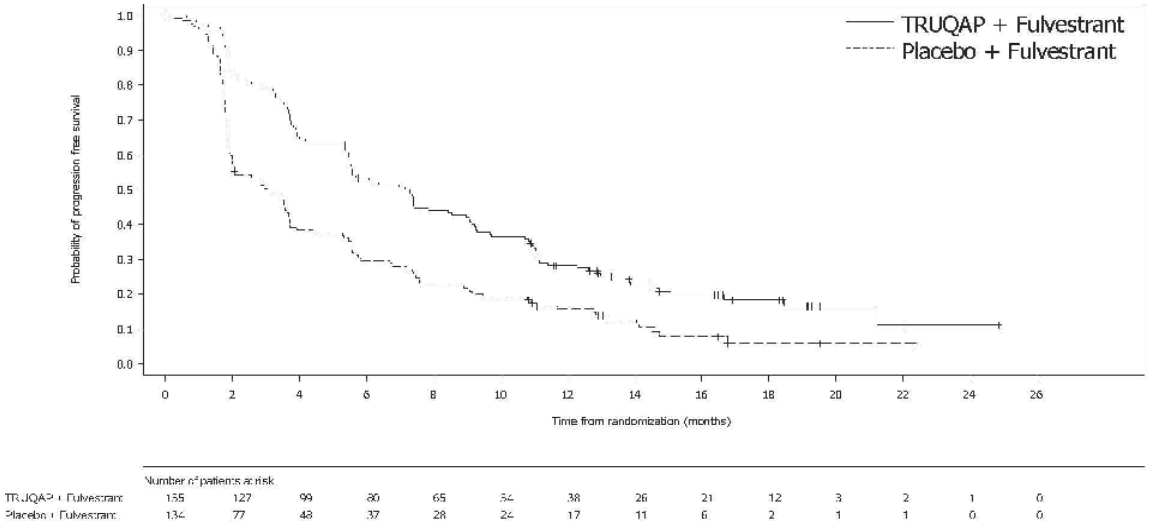
Partial response rate	23%	8%
Median DoR, months (95% CI)	10.2 (7.7, NC‡)	8.6 (3.8, 9.2)

* Stratified Cox proportional hazards model stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no).

† Stratified log-rank test stratified by presence of liver metastases (yes vs no), and prior use of CDK4/6 inhibitors (yes vs no).

‡ NC = not calculable

Figure 1: Kaplan-Meier Plot of Progression-Free Survival in CAPItello-291 (Investigator Assessment, Patients with PIK3CA/AKT1/PTEN-Altered Tumors)



PIK3CA/AKT1/PTEN alterations were identified by F1CDx / OncoScreen Plus™ as per the biomarker rules described below and patients allocated to the altered /non-altered subpopulations if one of more alterations were detected / not detected.

Table 8 Capivasertib Biomarker Rules

Gene (Transcript)	Variant Class	Biomarker Rules
PIK3CA (NM_006218)	Short Variant	C420R, E542K, E545A, E545D, E545G, E545K, E545Q, G1049R, H1047L, H1047R, H1047Y, M1043V, M1043I, N345K, Q546E, Q546K Q546P, Q546R, and R88Q alterations
AKT1 (NM_001014431)	Short Variant	Any short variant with protein effect E17K
PTEN (NM_000314)	Short Variant	Any short variants listed below: C124R, C124S, G129E, G129V, G129R, R130Q, R130G, R130L, R130P, C136R, C136Y, S170R and R173C
		Any nonsense (including stop codons), frameshift, or splice site alteration, including those that affect the start codon (i.e. M1?, M1T, M1fs*23).
	Copy Number Alteration	Any homozygous deletion of one or more exons, regardless of transcript
	Rearrangement	Any rearrangement that disrupts protein function, regardless of transcript Intragenic events including duplications of only part of the gene, deletions, or inversions Translocations, deletions, or inversions where one breakpoint is in *PTEN* and the other breakpoint is in another gene or intergenic region.

[a] *PTEN* Rearrangement not included in OncoScreen Plus™ biomarker rules

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

TRUQAP 160 mg

Beige film-coated, round, biconvex tablets debossed with ‘CAV’ above ‘160’ on one side and plain on the reverse-

TRUQAP 200 mg

Beige film-coated, capsule-shaped, biconvex, tablets debossed with ‘CAV 200’ on one side and plain on the reverse.

14.2 Storage and Handling

No Special storage conditions. Storage at room temperature is recommended.

. Keep out of the reach and sight of children.

15 MANUFACTURER

AstraZeneca AB

Södertälje, Sweden

16 LICENSE HOLDER

AstraZeneca (Israel) Ltd.

1 Atirei Yeda St.,

Kfar Saba 4464301

Approved on June 2024 according to MoH guidelines.