TRUQAP
(capivasertib)

1 NAME OF THE MEDICINAL PRODUCT

TRUQAP film-coated tablets, 160 mg and 200 mg

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 excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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.

For excipients, see section 6.1.

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 locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration following recurrence or progression on or after an endocrine-based regimen.

4.2 Posology and Method of administration

Patients with hormone receptor (HR) positive, HER2-negative advanced breast cancer should be selected for treatment with TRUQAP based on the presence of one or more PIK3CA/AKT1/PTEN genetic alterations using a validated test.

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.

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

In pre/peri-menopausal women, TRUQAP plus fulvestrant should be combined with a luteinizing hormone releasing hormone (LHRH) agonist. Refer to the approved Prescribing 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.

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 TRUQAP 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. 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 Table 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 diabetologist/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 diabetologist/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.

CTCAE Grade[b] and Fasting Glucose (FG)[c] values prior to TRUQAP dose	Recommendations[d]
Grade 4 > 500 mg/dL or > 27.8 mmol/L	Withhold TRUQAP and consult with diabetologist/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.

CTCAE Grade[a]	Recommendations
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 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 of TRUQAP for rash and other skin drug reactions

CTCAE Grade[a]	Recommendations
Grade 1	No TRUQAP dose adjustment required. Initiate emollients and consider adding an 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, interrupt TRUQAP. Resume at the same dose level once the rash becomes clinically tolerable. Persistent or recurrent: reduce TRUQAP by one lower dose. See Table 2.
Grade 3	Interrupt TRUQAP. Initiate appropriate dermatological treatment with topical steroid of moderate/ higher strength, non-sedating 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.

CTCAE Grade[a]	Recommendations
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 drug 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. Resume TRUQAP at the same dose.
Grade 3	Interrupt TRUQAP until symptoms improve to ≤ Grade 1. If symptoms improve within 28 days, restart TRUQAP at same dose. If recovery occurs after 28 days, resume Truqap at one lower dose level. See Table 2.
Grade 4	Permanently discontinue TRUQAP

[a] Grading according to CTCAE Version 5.0.

Co-administration with strong CYP3A4 inhibitors

Avoid concomitant use with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, the dose of TRUQAP should be reduced to 320 mg twice daily (equivalent to a total daily dose of 640 mg) for 4 days followed by 3 days off (see section 4.5).

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.

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, 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. TRUQAP should not 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.

4.4 Special warnings and special 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.

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).

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

<table>
<tr><th></th><th>Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with TRUQAP</th><th>Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes and treated with TRUQAP</th></tr>
<tr><td>At screening, before initiating treatment with TRUQAP</td><td colspan="2">Test for fasting glucose (FG) levels and HbA1c.

Optimise the patient’s level of blood glucose (see section 4.2 Table 3).</td></tr>
<tr><td rowspan="2">After initiating treatment with TRUQAP</td><td colspan="2">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.</td></tr>
<tr><td>Additional monitoring/self-monitoring may be required in accordance with the instructions of a healthcare professional.</td><td>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.</td></tr>
</table>

	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
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

Severe diarrhoea associated with dehydration occurred in patients who received TRUQAP.

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.

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 hypovolaemia and low electrolyte levels.

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.

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.

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 (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 medicinal products and other forms of interaction

The mechanism of drug-drug clinical interactions and study results are described in section 5.2.

Effect of Other Drugs on TRUQAP

Table 8 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).
Prevention or management	Avoid concomitant use with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce the dose of TRUQAP (see section 4.2).
Examples[b]	Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, saquinavir, ritonavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole. Intake of high doses of grapefruit should be avoided.
Moderate CYP3A Inhibitors	
Clinical impact	Concomitant use with a moderate CYP3A4 inhibitor increases capivasertib exposure, which may increase the risk of TRUQAP adverse reactions (see section 5.2).
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).
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).
Prevention or management	Avoid concomitant use of TRUQAP with strong CYP3A inducers.
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	Avoid concomitant use of TRUQAP with moderate CYP3A inducers.
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%.

Effect of TRUQAP on Other Drugs

Table 9 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, cyclosporine, 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). 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). 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 Pregnancy, lactation and fertility

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 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

There are no data from the use of TRUQAP in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Therefore, TRUQAP is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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). Breast-feeding should be discontinued during treatment with TRUQAP.

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 prescribing 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 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 Undesirable effects

Overall summary of the 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%).

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 10 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)
	Diabetic Ketoacidosis[4]	1 (0.3)	1 (0.3)	0	0
Nervous system disorders	Dysgeusia	21 (5.9)	0	4 (1.1)	0
Gastrointestinal disorders	Diarrhoea[5]	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[6]	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[7]	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

		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 (%)**
	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] 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 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).

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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other protein kinase inhibitors
ATC code: 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 *PIK3C*A, *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 C_{max} 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

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.

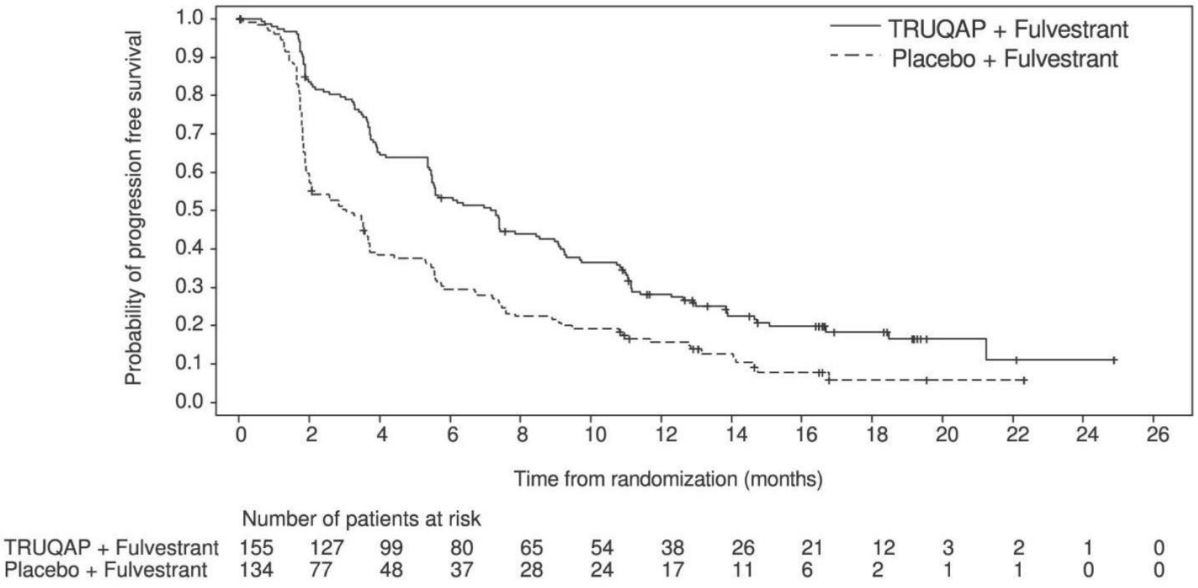
Efficacy results for *PIK3CA/AKT1/PTEN*-altered subgroup are presented in Table 11 and Figure 1. Results from the blinded independent review committee (BICR) assessment were consistent with the investigator assessed PFS results. Overall survival results were immature at the time of the PFS analysis (30% of the patients died).

Table 11 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)



Number of patients at risk

TRUQAP + Fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo + Fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

5.2 Pharmacokinetic properties

Capivasertib pharmacokinetics have been characterized 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.

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.

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.

Special populations

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 $\leq$ ULN and AST > ULN, or bilirubin > 1 ULN to $\leq$ 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 $\leq$ 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 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 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

Non-clinical/Repeat-dose toxicity

The major target organs or systems for toxicity were insulin signalling (increased levels of glucose and insulin in rats and dogs), the male reproductive organs (tubular degeneration in in 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).

Mutagenicity and carcinogenicity

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.

Reproductive toxicity

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.

Fertility

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

The names of inactive ingredients may vary according to region.

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

Refer to locally approved shelf life.

6.4 Special precautions for storage

Store in original package at or below 30°C.

6.5 Nature and contents of container

Not all presentations may be available in all markets.

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

HDPE bottle with a child-resistant closure. Pack size of 64 tablets.

PVC blister in child resistant wallet pack containing 16 film-coated tablets. Pack size of 64 tablets (4 blisters).

6.6 Instructions for use, handling and disposal

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

Product Owner

AstraZeneca AB
SE-151 85
Södertälje
Sweden

Date of revision of text

September 2024

09/BD/SG/VV-RIM-04944503 V4.0

P: VV-RIM-06445913 V1.0

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