TRUQAP® 160MG & 200MG FILM-COATED TABLETS
Capivasertib

1. NAME OF THE MEDICINAL PRODUCT

TRUQAP 160 mg film-coated tablets
TRUQAP 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRUQAP 160 mg film-coated tablets

Each film-coated tablet contains 160 mg of capivasertib.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablet).

TRUQAP 160 mg film-coated tablets

Round, biconvex, beige film-coated tablets debossed with 'CAV' above '160' on one side and plain on the reverse. Approximate diameter: 10 mm.

TRUQAP 200 mg film-coated tablets

Capsule-shaped, biconvex, beige film-coated tablets debossed with 'CAV 200' on one side and plain on the reverse. Approximate size: 14.5 mm (length), 7.25 mm (width).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following recurrence or progression on or after an endocrine-based regimen (see section 5.1).

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

For men, 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 physician experienced in the use of anticancer medicinal products.

Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with TRUQAP based on the presence of one or more *PIK3CA/AKT1/PTEN* -alterations which should be assessed by a IVD with the corresponding intended purpose. If the IVD is not available, an alternative validated test should be used.

Posology

The recommended dose of TRUQAP is 400 mg (two 200 mg tablets) twice daily, approximately 12 hours apart (total daily dose of 800 mg), for 4 days followed by 3 days off treatment. See 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.

TRUQAP should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. Refer to the Summary of Product Characteristics (SmPC) of fulvestrant for more information.

Missed dose
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.

Vomiting
If the patient vomits, an additional dose should not be taken. The next dose of TRUQAP should be taken at the usual time.

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

Table 2 TRUQAP dose reduction guidelines for adverse reactions

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

Hyperglycaemia

Table 3 Recommended dose modification for 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[e].
Grade 2 > 160-250 mg/dL or > 8.9-13.9 mmol/L	Withhold TRUQAP and initiate or intensify oral anti-diabetic treatment. 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 TRUQAP 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 a diabetologist. Initiate or intensify oral anti-diabetic treatment. Consider additional anti-diabetic medicinal products such as insulin[f], 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 a diabetologist. Initiate or intensify appropriate anti-diabetic treatment. Consider insulin[f], (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 diabetic ketoacidosis (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 for further recommendations on monitoring of glycaemia and other metabolic parameters.

[e] Consultation with a diabetologist should be considered when selecting the anti-diabetic medicinal product. A potential for hypoglycaemia with anti-diabetic medicinal product administration on non-TRUQAP dosing days

should be taken into account. Patients should also consider consultation with a dietician to make lifestyle changes that may reduce hyperglycaemia (see section 4.4).

Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of capivasertib. Dosing and management of patients receiving the metformin and capivasertib combination requires caution. Due to the potential interaction of metformin and capivasertib (caused by the inhibition of renal transporters [e.g. OCT2] involved in the excretion of metformin), when taking both capivasertib and metformin concurrently, it is recommended weekly monitoring of creatinine after initiation of metformin, for up to 3 weeks and then on Day 1 of each cycle thereafter.

Metformin should only be given on the days when capivasertib is also administered (the half-life of capivasertib is approximately 8 hours) and should be withdrawn when treatment with capivasertib is withdrawn, unless otherwise clinically indicated.

[f] There is limited experience in patients receiving insulin when being treated with TRUQAP.

Diarrhoea

Secondary prophylaxis should be considered in patients with recurrent diarrhoea (see section 4.4).

Table 4 Recommended dose modification for TRUQAP for diarrhoea

CTCAE Grade[a]	Recommendations
Grade 1	No TRUQAP dose adjustment required. Initiate appropriate anti-diarrhoeal therapy, maximise supportive care and monitor as clinically indicated.
Grade 2	Initiate or intensify appropriate anti-diarrhoeal treatment, monitor the patient and if 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 the next 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 symptom does not improve to ≤ Grade 1 in 28 days permanently discontinue TRUQAP.
Grade 4	Permanently discontinue TRUQAP.

[a] Grade according to the NCI CTCAE Version 5.0.

Rash and other skin drug reactions

Consultation with a dermatologist for all grades of skin drug reactions regardless of the severity should be considered. In patients with persistent rash and/or previous occurrence of grade 3 rash, secondary prophylaxis should be considered by continuing oral antihistamines and/or topical steroids (see section 4.4).

Table 5 Recommended dose modification for TRUQAP for rash and other skin drug reactions

CTCAE Grade[a]	Recommendations
Grade 1	No TRUQAP dose adjustment required. Initiate emollients and consider adding oral non-sedating antihistamine treatment as clinically indicated to manage symptoms.
Grade 2	Initiate or intensify topical steroid treatment and consider non-sedating oral antihistamines. If no improvement with treatment, 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, 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.
Grade 4	Permanently discontinue TRUQAP.

[a] Grading according to CTCAE Version 5.0.

Other toxicities

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

CTCAE Grade[a]	**Recommendations**
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 and moderate CYP3A4 inhibitors

Co-administration of TRUQAP with strong CYP3A4 inhibitors should be avoided. If co-administration cannot be avoided, the dose of TRUQAP should be reduced to 320 mg twice daily (equivalent to a total daily dose of 640 mg).

TRUQAP dose should be reduced to 320 mg twice daily (equivalent to a total daily dose of 640 mg) when co-administered with moderate CYP3A4 inhibitors.

After discontinuation of a strong or moderate CYP3A4 inhibitor, TRUQAP dosage (after 3 to 5 half-lives of the inhibitor) that was taken prior to initiating the strong or moderate CYP3A4 inhibitor should be resumed.

See section 4.5 for further information.

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
The safety and efficacy of TRUQAP in children aged 0-18 years of age has not been established. No data are available.

Method of administration

TRUQAP is for oral use. The tablets can be taken with or without food (see section 5.2). They should be swallowed whole with water and not chewed, crushed, dissolved, or divided. No tablet should be ingested if it is broken, cracked, or otherwise not intact because these methods have not been studied in clinical trials.

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

The safety and efficacy of TRUQAP in patients with pre-existing Type 1 diabetes or Type 2 diabetes requiring insulin and/or in patients with HbA1C > 8.0% (63.9 mmol/mol) has not been studied as these patients were excluded from the phase III clinical study. This study included 21 (5.9%) patients in the TRUQAP plus fulvestrant arm with HbA1C ≥ 6.5%. Hyperglycaemia was more frequently reported in patients with a baseline HbA1C ≥ 6.5% (33.3% of patients) than those with a baseline HbA1C < 6.5% (16.0%). Severe hyperglycaemia, associated with diabetic ketoacidosis (DKA) and with fatal outcomes occurred in patients treated with TRUQAP (see section 4.8). DKA can occur at any time during TRUQAP treatment. In some reported cases, DKA developed in less than 10 days. Patients with history of diabetes mellitus may require intensified anti-diabetic treatment and should be closely monitored. Consultation with a diabetologist or a healthcare professional experienced in the treatment of hyperglycaemia is recommended for patients with diabetes.

Before initiating treatment with TRUQAP, patients should be informed about TRUQAP's potential to cause hyperglycaemia (see section 4.8) and requested 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, or 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 nonspecific 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.

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[1]</th></tr>
<tr><td>At screening, before initiating treatment with TRUQAP</td><td colspan="2">Test for fasting blood glucose (FG) levels, HbA1c, and optimise the patient's level of blood glucose (see 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 treatment start and monthly thereafter.

It is recommended to test FG pre-dose at Day 3 or 4 of the dosing week.

HbA1c should be monitored every 3 months.</td></tr>
<tr><td>Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.</td><td>Monitor/self-monitor 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*.</td></tr>
</table>

		Additional HbA1c testing is recommended at week 4 with diabetes, pre-diabetes, or hyperglycaemia at baseline.
If hyperglycaemia develops after initiating treatment with TRUQAP	Monitor fasting glucose as clinically indicated (at least twice weekly, i.e. on days on and off capivasertib treatment) until FG decreases to baseline levels[2]. Consultation with a healthcare practitioner with expertise in the treatment of hyperglycaemia should be considered. Based on the severity of hyperglycaemia, TRUQAP dosing may be interrupted, reduced, or permanently discontinued (see section 4.2, Table 3).	
	During treatment with anti-diabetic medication, FG should be monitored for at least once a week for 2 months, followed by once every 2 weeks or as clinically indicated[2].	
[*] All glucose monitoring should be performed at the physician's discretion as clinically indicated. [1] More frequent FG testing is required in patients with medical history of diabetes mellitus, in patients without prior history of diabetes mellitus and showing FG of > ULN 160 mg/dL (> ULN 8.9 mmol/L) during treatment, in patient with concomitant use of corticosteroids, or in those with intercurrent infections, or other conditions which may require intensified glycaemia management to prevent worsening of impaired glucose metabolism and potential complications, namely diabetic ketoacidosis. [2] It is recommended to test FG pre-dose at Day 3 or 4 of the dosing week.		

Diarrhoea

Diarrhoea has been reported in the majority of the patients treated with TRUQAP (see section 4.8). Clinical consequences of diarrhoea may include dehydration, hypokalaemia and acute kidney injury, which have all, together with cardiac arrhythmias (with hypokalaemia as risk factor) been reported during treatment with TRUQAP. 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-diarrhoeal 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 drug reactions

Skin drug 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 drug reactions, the dosing may be interrupted, reduced, or permanently discontinued (section 4.2, Table 5). Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

Patients excluded from the study

The efficacy and safety of this medicinal product have not been studied in patients with symptomatic visceral disease. The patients with history of clinically significant cardiac disease including QTcF > 470 msec, any factors that increased the risk of QTc prolongation or risk of arrhythmic events or risk of cardiac function impairment, or patients with pre-existing Type 1 diabetes and Type 2 diabetes requiring insulin, and patients with HbA1C > 8.0% (63.9 mmol/mol) were excluded from CAPItello-291. This should be considered if TRUQAP is prescribed in these patients.

Other medicinal products

Co-administration of strong or moderate CYP3A4 inhibitors with TRUQAP may lead to increased capivasertib exposure and consequently a higher risk of toxicity. Refer to section 4.2 regarding TRUQAP dose modification when co-administered with CYP3A4 inhibitors.

On the contrary, co-administration of strong and moderate CYP3A4 inducers may lead to decreased capivasertib exposure. Concomitant administration of strong and moderate CYP3A4 inducers and TRUQAP should be avoided.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. *In vivo*, capivasertib is a weak, time-dependent inhibitor of CYP3A.

Medicinal products that may increase capivasertib plasma concentrations

Strong CYP3A4 inhibitors
Co-administration of TRUQAP with strong CYP3A4 inhibitors increases capivasertib concentration, which may increase the risk of TRUQAP toxicity. Co-administration with strong CYP3A4 inhibitors should be avoided (e.g. boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole, grapefruit or grapefruit juice). If co-administration cannot be avoided, TRUQAP dose should be reduced (see section 4.2). Co-administration of multiple 200 mg doses of the strong CYP3A4 inhibitor itraconazole increased capivasertib total exposure (AUC_{inf}) and the peak concentration (C_{max}) by 95% and 70%, respectively, relative to capivasertib given alone.

Moderate CYP3A4 inhibitors
Co-administration of TRUQAP with moderate CYP3A4 inhibitors increases capivasertib concentration, which may increase the risk of TRUQAP toxicity. TRUQAP dose should be reduced when co-administered with moderate CYP3A4 inhibitor (e.g aprepitant, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole, fluvoxamine, tofisopam, verapamil) (see section 4.2).

Medicinal products that may decrease capivasertib plasma concentrations

Strong CYP3A4 inducers
Co-administration of TRUQAP with strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided. Co-administration of capivasertib with strong CYP3A4 inducer enzalutamide decreased the capivasertib AUC by approximately 40% to 50%.

Moderate CYP3A4 inducers
Co-administration of capivasertib with moderate CYP3A4 inducer has the potential to decrease the concentration of capivasertib. This may reduce the efficacy of TRUQAP. Co-administration of moderate CYP3A4 inducers should be avoided (e.g. bosentan, cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, modafinil, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine).

Medicinal products whose plasma concentrations may be altered by capivasertib

Substrates of CYP3A
Concentration of medicinal products that are primarily eliminated via CYP3A metabolism may increase when coadministered with TRUQAP which may then lead to increased toxicity depending on their therapeutic window. Capivasertib increased the midazolam AUC by 15% to 77% and is therefore a weak CYP3A inhibitor (see section 5.2). Dose adjustment may be required for medicinal products that are primarily eliminated via CYP3A metabolism and have narrow therapeutic window (e.g. carbamazepine, cyclosporine, fentanyl, pimozide, simvastatin, tacrolimus). The SmPC of the other medicinal products should be consulted for the recommendations regarding co-administration with weak CYP3A4 inhibitors.

CYP2D6 substrates with a narrow therapeutic index
In vitro evaluations indicated that capivasertib has a potential to inhibit the activities of CYP2D6 enzymes. Capivasertib should be used with caution in combination with sensitive substrates of CYP2D6 enzymes which exhibit a narrow therapeutic index because capivasertib may increase the systemic exposure of these substrates.

CYP2B6 substrates with a narrow therapeutic index
In vitro evaluations indicated that capivasertib has a potential to induce the activities of CYP2B6 enzymes. Capivasertib should be used with caution in combination with sensitive substrates of CYP2B6 enzymes which exhibit a narrow therapeutic index (e.g. bupropion) because capivasertib may decrease the systemic exposure of these substrates.

UGT1A1 substrates with a narrow therapeutic index
In vitro evaluations indicated that capivasertib has a potential to inhibit the activities of UGT1A1 enzymes. Capivasertib should be used with caution in combination with sensitive substrates of UGT1A1 enzymes which exhibit a narrow therapeutic index (e.g. irinotecan) because capivasertib may increase the systemic exposure of these substrates.

Interactions with hepatic transporters (BCRP, OATP1B1, OATP1B3)
The exposure of medicinal products that are sensitive to inhibition of BCRP, OATP1B1 and/or OATP1B3, if they are metabolised by CYP3A4, may increase by co-administration with TRUQAP. This may lead to increased toxicity. Depending on their therapeutic window, dose adjustment may be required for medicinal products that are sensitive to inhibition of BCRP, OATP1B1 and/or OATP1B3 if they are metabolised by CYP3A4 (e.g. simvastatin). The SmPC of the other medicinal products should be consulted for the recommendations regarding co-administration with CYP3A4, BCRP, OATP1B1 and OATP1B3 inhibitors.

Interactions with renal transporters (MATE1, MATE2K, OCT2)
The exposure of medicinal products that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by co-administration with TRUQAP. This may lead to increased toxicity. Depending on their therapeutic window, dose adjustment may be needed for medicinal products that are sensitive to inhibition of MATE1, MATE2K and OCT2 (e.g. dofetilide, procainamide). The SmPC of the other medicinal products should be consulted for the recommendations regarding co-administration with MATE1, MATE2K and/or OCT2 inhibitors. Transient serum creatinine increases may be observed during treatment with TRUQAP due to inhibition of OCT2, MATE1 and MATE2K by capivasertib.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/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. Re-testing should be considered throughout treatment.

Patients should be advised to use effective contraception during the use of 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 breast-fed 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, no adverse effect on female reproductive organs was observed, but the effect on female fertility in rats was not studied. Capivasertib has resulted in testicular toxicity and may impair fertility in males of reproductive potential (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 may have a minor influence on the ability to drive and use machines because fatigue, dizziness and syncope have been reported during treatment with capivasertib (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The summary of safety profile of TRUQAP is based on data from 355 patients who received TRUQAP plus fulvestrant in the phase III (CAPItello-291) study. The median duration of exposure to capivasertib in CAPItello-291 was 5.42 months, with 27% patients exposed ≥ 12 months.

The most common adverse reactions were diarrhoea (72.4%), rash (40.3%), nausea (34.6%), fatigue (32.1%), vomiting (20.6%), stomatitis (17.2%), hyperglycaemia (17.2%), headache (16.9%) and decreased appetite (16.6%).

The most common grade 3 or 4 adverse reactions were rash (12.4%), diarrhoea (9.3%), hyperglycaemia (2.3%), hypokalaemia (2.3%), anaemia (2.0%) and stomatitis (2.0%).

Serious adverse reactions were seen in 7.0% of patients receiving TRUQAP plus fulvestrant. Most common serious adverse reactions reported in patients receiving TRUQAP plus fulvestrant included rash (2.3%), diarrhoea (1.7%) and vomiting (1.1%).

Dose reductions due to adverse reactions were reported in 17.7% of patients. The most common adverse reactions leading to dose reduction of TRUQAP were diarrhoea (7.9%) and rash (4.5%).

Treatment discontinuation due to adverse reactions occurred in 9.9% of patients. The most common adverse reactions leading to treatment discontinuation were rash (4.5%), diarrhoea (2%) and vomiting (2%).

Tabulated list of adverse reactions

Table 8 lists the adverse reactions based on pooled data from patients treated with TRUQAP plus fulvestrant in clinical studies at the recommended dose.

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 <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).

Table 8 Adverse drug reactions observed in patients treated with TRUQAP

MedDRA SOC	MedDRA term	Any grade (%)
Infections and infestations	Urinary tract infection[1]	Very common
Blood and lymphatic system disorders	Anaemia	Very common
Immune system disorders	Hypersensitivity[2]	Common
Metabolism and nutrition disorders	Hyperglycaemia[3]	Very common
	Decreased appetite	Very common
	Hypokalaemia[4]	Common
	Diabetic ketoacidosis[5]	Uncommon
Nervous system disorders	Headache	Very common
	Dysgeusia	Common
	Dizziness	Common
	Syncope	Common
Renal and urinary disorders	Acute kidney injury	Common
Gastrointestinal disorder	Dry Mouth	Common
	Abdominal pain	Common
	Diarrhoea[2]	Very common
	Nausea	Very common
	Vomiting	Very common

MedDRA SOC	MedDRA term	Any grade (%)
	Stomatitis[6]	Very common
	Dyspepsia	Common
Skin and subcutaneous tissue disorders	Rash[7]	Very common
	Pruritus	Very common
	Dry skin	Common
	Erythema multiforme	Common
	Drug eruption	Uncommon
	Dermatitis	Uncommon
	Dermatitis exfoliative generalised	Uncommon
	Toxic skin eruption	Uncommon
General disorders and administration site conditions	Fatigue[8]	Very common
	Mucosal inflammation	Common
	Pyrexia[9]	Common
Investigations	Blood creatinine increased	Common
	Weight Decreased	Common
	Glycosylated haemoglobin increased	Common

[1] Urinary tract infection includes urinary tract infection and cystitis.
[2] Includes other related terms.
[3] Hyperglycaemia includes blood glucose increased, diabetes mellitus, hyperglycaemia, type 2 diabetes mellitus.
[4] Hypokalaemia includes blood potassium decreased and hypokalaemia.
[5] Diabetic ketoacidosis includes diabetic ketoacidosis and ketoacidosis.
[6] Stomatitis includes aphthous ulcer, mouth ulceration and stomatitis.
[7] Rash includes erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.
[8] Fatigue includes asthenia and fatigue.
[9] Pyrexia includes body temperature increased and pyrexia.

Description of selected adverse reactions

Hyperglycaemia
Hyperglycaemia of any grade occurred in 61 (17.2%) patients and grade 3 or 4 occurred in 8 (2.3%) patients receiving TRUQAP. The median time to first occurrence of hyperglycaemia was 15 days (range: 1 to 367). In the study, dose reduction was required in 2 (0.60%) patients and 1 (0.30%) patient discontinued treatment due to hyperglycaemia. In the 61 patients with hyperglycaemia, 29 (47.5%)

patients were treated using anti-hyperglycaemic medication (including insulin in 16.4%). See section 4.4.

Diarrhoea
Diarrhoea occurred in 257 (72.4%) patients receiving TRUQAP. Grade 3 and/or 4 diarrhoea occurred in 33 (9.3%) patients. The median time to first occurrence was 8 days (range 1 to 519). 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. The median time to first occurrence of rash was 12 days (range 1-226). Grade 3 and/or 4 occurred in 44 (12.4%) of patients who received capivasertib. Erythema multiforme occurred in 6 (1.7%) patients and the highest grade was grade 3 in 3 (0.8%) of the patients. Dermatitis exfoliative generalised occurred in 2 (0.6%) patients, these events were grade 3 in severity. Dose reduction was required in 16 (4.5%) patients and 16 (4.5%) patients discontinued TRUQAP due to rash.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is currently no specific treatment in the event of an overdose with TRUQAP. Higher than the indicated dosing of capivasertib can increase risk of capivasertib adverse reactions, including diarrhoea. Physicians should follow general supportive measures and patients should be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, 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 *AKT1*, loss of Phosphatase and Tensin Homolog (PTEN) function and mutations in the catalytic subunit of PI3K (*PIK3CA*).

Capivasertib reduces growth of cell lines derived from solid tumours and haematological disease, including breast cancer cell lines with and without *PIK3CA* or *AKT1* mutations, or *PTEN* alterations.

Treatment with capivasertib and fulvestrant demonstrated anti-tumour response in a range of ER+ human breast cancer PDX models representative of different breast cancer subsets. This included models with and without detectable mutations or alterations in *PIK3CA*, *PTEN* or *AKT1*.

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.

Clinical efficacy

CAPItello-291 was a randomised, double-blind, placebo-controlled study that enrolled 708 patients, designed to study the efficacy and safety of TRUQAP in combination with fulvestrant in adult females, pre- or post-menopausal, and adult males with locally advanced (inoperable) or metastatic ER-positive and HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) breast cancer of which 289 patients had tumors with one or more eligible *PIK3CA/AKT1/PTEN* alterations 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.

Patients were randomised 1:1 to receive either 400 mg of TRUQAP (N=355) or placebo (N=353) given twice daily for 4 days followed by 3 days off treatment each week of 28-day treatment cycle. Fulvestrant 500 mg was administered on cycle 1 days 1 and 15 and then at day 1 of a 28-day cycle. Pre- or perimenopausal women were treated with an LHRH agonist. Randomisation was stratified by presence of liver metastases, prior treatment with CDK4/6 inhibitors and geographical region. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. A tumour sample was collected prior to randomisation to determine *PIK3CA/AKT1/PTEN* alteration status retrospectively by central testing.

Demographic and baseline characteristics were well balanced between arms. Of the 708 patients, the median age was 58 years (range 26 to 90 and 30.7% were over 65 years of age); 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- or perimenopausal. 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.

At the data cutoff date (DCO) of 15 August 2022, the study showed statistically significant improvement in PFS for patients receiving TRUQAP plus fulvestrant compared to patients receiving placebo plus fulvestrant, in both the overall population and the *PIK3CA/AKT1/PTEN*-altered subgroup (see table 9). An exploratory analysis of PFS in the 313 (44%) patients whose tumours did not have a *PIK3CA/AKT1/PTEN* alterations 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 tumours have *PIK3CA/AKT1/PTEN* alteration. PFS results by investigator assessment were supported by consistent results from a blinded independent central review (BICR) assessment. The investigator-assessed ORR in patients receiving TRUQAP plus fulvestrant and placebo plus fulvestrant was 22.9% and 12.2%, respectively, in the overall population and 28.8% and 9.7%, respectively, in the altered subgroup.

A prespecified interim analysis of OS (DCO 15 April 2024, 59% of patients had died) showed a HR of 0.88 (95% CI: 0.65, 1.19) in the *PIK3CA/AKT1/PTEN*-altered subgroup.

Efficacy results are presented in Table 9 and Figure 1.

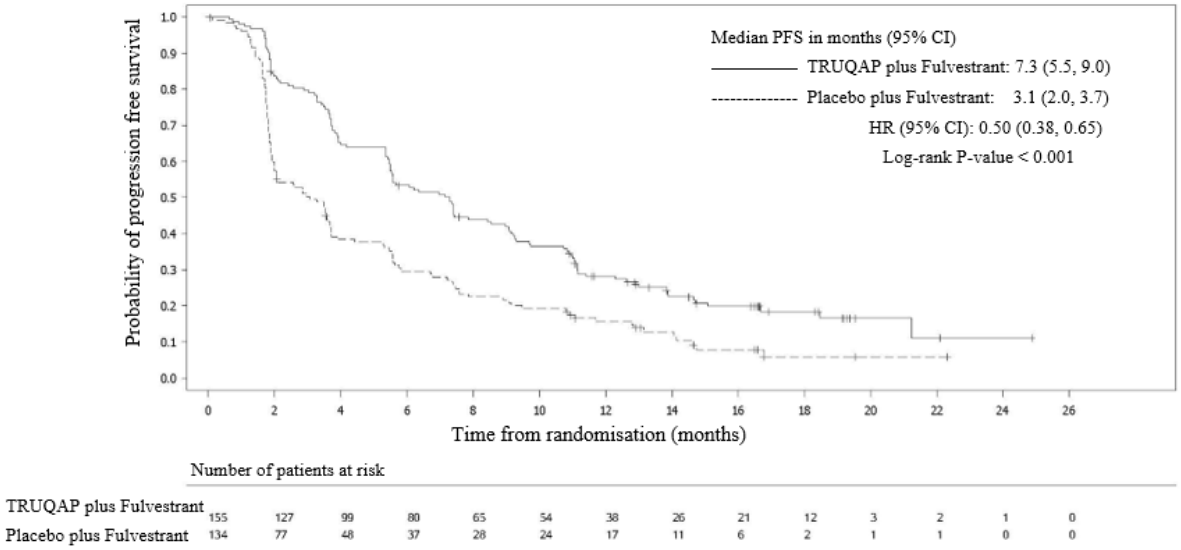
Table 9 Progression-free survival, by investigator assessment in *PIK3CA/AKT1/PTEN*-altered subgroup

	***PIK3CA/AKT1/PTEN*-altered subgroup N = 289**	
	TRUQAP plus fulvestrant N = 155	**Placebo plus fulvestrant N = 134**
Number of PFS events – n (%)	121 (78.1)	115 (85.8)
Median PFS months (95% CI)	7.3 (5.5, 9.0)	3.1 (2.0, 3.7)
Hazard ratio (95% CI)[a]	0.50 (0.38, 0.65)	
p-value[b]	< 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 – CAPItello-291 (investigator assessment, *PIK3CA/AKT1/PTEN*-altered subgroup)



5.2 Pharmacokinetic properties

Capivasertib pharmacokinetics have been characterised in healthy subjects and patients with solid tumours. The systemic exposure (AUC and C_{max}) increased proportionally over the dose range of 80 to 800 mg range after single dose administration in patients. After multiple-dose administration of 80 to

600 mg twice daily, the AUC increased slightly more than dose proportional. Following intermittent dosing of capivasertib 400 mg twice daily, 4 days on and 3 days off, the capivasertib steady-state concentrations with AUC of 8 069 hng/mL (37%) and C_{max} of 1 371 ng/mL (30%) are predicted to be attained on the 3rd and 4th dosing day of 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 meal (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 was 2.6 L/Kg 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 h. The mean total plasma clearance was 38 L/h after a single IV 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 race, age, gender and weight
Based on population pharmacokinetic analysis, AUC and C_{max} showed that race (including White and Japanese patients), gender or age did not significantly impact the capivasertib exposure. There was a statistically significant correlation of apparent oral clearance of capivasertib to body weight. Compared to a patient with a body weight of 66 kg, a 47 kg patient is predicted to have 12% higher AUC. There is no basis for dose modification based on body weight as the predicted effect on capivasertib exposure was small.

Renal impairment
Based on population pharmacokinetic analyses, AUC and C_{max} were 1% higher in patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), compared to patients with normal renal function. AUC and C_{max} were 16% higher in patients with moderate renal impairment (creatinine clearance 30 to 59 mL/min), compared to patients with normal renal function.
There is no data in severe renal impairment or end-stage renal disease (creatinine clearance < 30 ml/min).

Hepatic impairment
Based on population pharmacokinetic analyses, AUC and C_{max} were 5% higher in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1 ULN to ≤ 1.5 ULN), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST ≤ ULN). AUC was 17% and C_{max} was 13% higher 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 interactions
Co-administration of a single dose of capivasertib 400 mg after repeated dosing of acid-reducing agent rabeprazole 20 mg BID for 3 days in healthy subjects did not result in clinically relevant changes of the capivasertib exposure.

In vitro studies have demonstrated that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Results of clinical drug-drug interaction (DDI) studies investigating potential DDI based on CYP3A4 interactions (itraconazole and enzalutamide) are included in section 4.5 above. Clinical DDI studies investigating potential DDIs based on UGT2B7 interactions have not been performed.

Capivasertib inhibited CYP2C9, CYP2D6, CYP3A4 and UGT1A1 and induced CYP1A2, CYP2B6 and CYP3A4 metabolising enzymes in *in vitro* studies. It also inhibited BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K drug transporters *in vitro*. Results of clinical DDI study investigating potential DDIs based on CYP3A4 interactions (midazolam) are included in section 4.5 above. Clinical DDI studies investigating potential DDIs based on CYP1A2, CYP2B6, CYP2C9, CYP2D6, UGT1A1, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K interactions have not been performed.

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 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).

Lens degeneration was observed in male rats in the 2-year rat carcinogenicity study at exposures lower than those in humans (0.1 times) at the recommended dose of 400 mg twice daily (based on total AUC) and may be related to elevated glucose levels.

Cardiovascular effects (QTc interval prolongation, increased cardiac contractility, and decreased blood pressure) were seen in dogs at plasma concentrations approximately 1.4 to 2.7 times the expected clinical exposure in humans at the recommended dose of 400 mg twice daily (based on unbound C_{max}).

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.

In a 2-year rat carcinogenicity study there was an increased incidence and/or severity of islet of Langerhans hypertrophy/hyperplasia (males and females) and neoplastic findings in the testis in males. Findings were observed at exposures lower than those in humans (0.2 to 0.5 times) at the recommended dose of 400 mg twice daily (based on total AUC).

Reproductive toxicity

Embryofoetal/Developmental toxicity

In a rat embryofoetal study, capivasertib caused an increase in post implantation loss, an increase in early embryonic deaths, together with reduced gravid uterine and foetal weights, and minor foetal 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 has resulted in testicular toxicity and may impair fertility in males of reproductive potential. Effects on female fertility have not been studied in animals. In females, repeat-dose toxicity studies have reported some weight changes of the uterus in rats which were attributed to estrous cycle changes. Histopathological examination conducted in rat and dog studies did not show any treatment-related effects on female reproductive organs, which may be indicative of an adverse effect on female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460i)
Calcium hydrogen phosphate
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film coating

Hypromellose
Titanium dioxide (E171)
Macrogol 3350
Polydextrose
Copovidone
Triglycerides, medium chain
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the expiry date on the outer carton.

6.4 Special precautions for storage

Store in original package below 30°C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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

7. MANUFACTURED BY

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8. DATE OF REVISION OF THE TEXT

19 January 2026
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