▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Truqap 160 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 160 mg capivasertib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets (tablet)

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Truqap is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following recurrence or progression on or after an endocrine based regimen (see section 5.1).

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 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*-alterations using a validated test.

Posology

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

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 intramuscularly on Days 1, 15, and 29, and once monthly thereafter. Refer to the approved Summary of Product Characteristics (SmPC) of fulvestrant for more information.

In pre/perimenopausal women, Truqap plus fulvestrant should be combined with a luteinizing hormone releasing hormone (LHRH) agonist. For men, consider administering a LHRH agonist according to current clinical practice standards. Refer to the approved Summary of Product Characteristics (SmPC) 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. If a dose is missed and more than 4 hours have passed, 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.

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

Table 2 Truqap dose reduction guidelines for adverse reactions

Truqap	Dose and Schedule	Number and Strength of Tablets
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

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	Initiate or intensify oral anti-diabetic treatment. Withhold Truqap until fasting glucose (FG) level decrease to ≤ 160 mg/dl (or ≤ 8.9 mmol/L). If recovery occurs in ≤28 days, resume Truqap at the same dose and maintain initiated or intensified anti-diabetic treatment. If improvement to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) is reached in more than 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 until fasting glucose (FG) level decrease to ≤ 160 mg/dl (or ≤ 8.9 mmol/L) 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.

CTCAE Grade[b] and Fasting Glucose (FG)[c] values prior to Truqap dose	Recommendations[d]
	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).
[f] There is limited experience in patients receiving insulin when being treated with Truqap.

Diarrhoea

Consider secondary prophylaxis 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 and monitor as clinically indicated. Withhold Truqap dose for up to 28 days until recovery to ≤ Grade 1 and resume Truqap dosing at same dose or one lower dose level as clinically indicated. If Grade 2 diarrhoea is persistent or recurring, maintain appropriate medical therapy and restart Truqap at one lower dose level, as clinically indicated.
Grade 3	Withhold Truqap until recovery to ≤ Grade 1. Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. If recovery occurs in ≤ 28 days, resume Truqap at one lower dose level. If recovery to ≤ Grade 1 in > 28 days, permanently discontinue Truqap.
Grade 4	Permanently discontinue Truqap.

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

Cutaneous adverse drug reactions

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

Table 5 Recommended dose modification for Truqap for cutaneous adverse 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	Withhold Truqap until recovery to ≤ Grade 1. Initiate or intensify topical steroid treatment and consider non-sedating oral antihistamines. If recovery occurs in ≤ 28 days, resume Truqap at the same dose level. If persistent or recurrent: restart Truqap by one dose level.
Grade 3	Withhold Truqap until recovery to ≤ Grade 1. Initiate appropriate dermatological treatment with topical steroid of moderate/higher strength,-non-sedating oral antihistamines and/or systemic steroids. If recovery occurs in ≤ 28 days, restart Truqap on one lower dose level. If the symptoms do not improve to ≤ Grade 1 within 28 days discontinue Truqap. In patients with reoccurrence of intolerable Grade 3 rash, permanently discontinue Truqap.
Grade 4	Permanently discontinue Truqap.

[a] Grading according to CTCAE Version 5.0.

Other toxicities

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

CTCAE Grade[a]	Recommendations
Grade 1	No Truqap dose adjustment required, initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Withhold Truqap until symptoms improve to ≤ Grade 1.
Grade 3	Withhold Truqap until symptoms improve to ≤ Grade 1. If symptoms improve, restart

	Truqap at same dose or one lower dose level as clinically appropriate.
Grade 4	Permanently discontinue Truqap.

[a] Grading according to CTCAE Version 5.0

Co-administration with strong and moderate CYP3A4 inhibitors

The dose of Truqap should be reduced to 320 mg twice daily, 4 days on, 3 days off when concomitantly used with strong or moderate CYP3A4 inhibitors (see section 4.5).

Special populations

Elderly population

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 (creatinine clearance 60 to 89 mL/min) or moderate (creatinine clearance 30 to 59 mL/min) renal impairment. Truqap is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min), 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 (bilirubin ≤ULN and AST > ULN or bilirubin >1.0x - 1.5xULN). Limited data are available for patients with moderate hepatic impairment (bilirubin >1.5x - 3.0x ULN); 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 adverse effects due to potential increase in capivasertib exposure. Truqap is not recommended for patients with severe hepatic impairment (bilirubin >3.0x ULN), 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.

Method of administration

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

4.3 Contraindications

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 the start and during treatment with Truqap, in accordance with the intervals recommended 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*.

Additional HbA1c testing is recommended at week 4 with diabetes, pre-diabetes, or hyperglycaemia at baseline.</td></tr>
<tr><td rowspan="2">If hyperglycaemia develops after initiating treatment with Truqap</td><td colspan="2">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).</td></tr>
<tr><td colspan="2">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].</td></tr>
<tr><td colspan="3">* 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 patients 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.</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[1]**
[2] It is recommended to test FG pre-dose at Day 3 or 4 of the dosing week.		

Diarrhoea

Diarrhoea has been frequently reported in patients treated with Truqap (see section 4.8), including severe diarrhoea associated with dehydration and Grade ≥ 3 hypokalaemia. 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.

Cutaneous adverse drug reactions

Cutaneous adverse drug reactions, including erythema multiforme and dermatitis exfoliative generalised have been reported in patients receiving Truqap. Patients should be advised of the risk of severe skin reactions and should be monitored for signs and symptoms of rash or dermatitis. Based on severity of skin drug reactions, Truqap 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 receiving bisphosphonates or RANK-ligand inhibitors

Patients with metastatic cancer receiving bisphosphonates or RANK-ligand inhibitors prior to or during treatment with capivasertib should be closely monitored for signs or symptoms of jaw osteonecrosis. Patients should be advised to promptly report any new or worsening oral symptoms including dental mobility, pain or swelling, non-healing of mouth sores or discharge. In patients who develop osteonecrosis of the jaw, standard medical management should be initiated.

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

Medicinal products that may increase capivasertib plasma concentrations

Strong CYP3A4 inhibitors

Co-administration of multiple 200 mg doses of the strong CYP3A4 inhibitor itraconazole with a single 80 mg capivasertib dose increased capivasertib total exposure (AUC_{inf}) and the peak concentration (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 52-56% and 30-35%, respectively. Co-administration of Truqap with strong CYP3A4 inhibitors increases capivasertib concentration, which may increase the risk of Truqap toxicity. Reduce the dose of Truqap when co-administered with strong CYP3A4 inhibitors (e.g., Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, ensitrelvir, idelalisib, indinavir, itraconazole, josamycin, ketoconazole, lonafarnib, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, ritonavir, telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole, grapefruit or grapefruit juice) (see section 4.2).

Moderate CYP3A4 inhibitors

Co-administration of Truqap with moderate CYP3A4 inhibitors is predicted to increase capivasertib concentration, which may increase the risk of Truqap toxicity. Reduce the dose of Truqap when coadministered with moderate CYP3A4 inhibitors (e.g., aprepitant, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole fluvoxamine, tofisopam, verapamil) (see section 4.2).

UGTB27 inhibitors

Coadministration of Truqap with UGT2B7 inhibitors (e.g. probenecid, valproic acid) has the potential to increase capivasertib concentration, which may increase the risk of Truqap toxicity.

Medicinal products that may decrease capivasertib plasma concentrations

Strong CYP3A4 inducers

Co-administration of capivasertib with strong CYP3A4 inducer enzalutamide decreased the capivasertib AUC by approximately 40% to 50% and rifampicin is predicted to decrease capivasertib AUC by 70%. Co-administration of Truqap with strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampicin, St. John’s wort) is not recommended.

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 Truqap with moderate CYP3A4 inducers is not recommended (e.g., bosentan, cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, modafinil, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine).

UGT2B7 inducers

Coadministration of Truqap with UGT2B7 inducers (e.g. rifampicin) has the potential to decrease capivasertib concentration. This may potentially reduce the efficacy of Truqap.

Interaction with acid reducing agents

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. The capivasertib AUC and C_{max} decreased by 6% and 27% respectively when co-administered with 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.

In vitro studies

In vitro studies have demonstrated that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Based on physiologically based pharmacokinetic models, the predicted increase in capivasertib AUC by the moderate inhibitors verapamil and erythromycin is 40%, with less impact on C_{max}. Co-administration with the UGT2B7 inhibitor probenecid is predicted to cause an increase in capivasertib AUC of 37% over a dosing cycle.

Medicinal products whose plasma concentrations may be altered by capivasertib

Substrates of CYP3A

Concentration of drugs that are primarily eliminated via CYP3A metabolism may increase when co-administered 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 drugs that are primarily eliminated via CYP3A metabolism and have narrow therapeutic window (e.g., carbamazepine, cyclosporine, fentanyl, pimozide, simvastatin, tacrolimus). Refer to specific guidance in the prescribing information for these drugs.

Substrates of CYP2B6

Concentration of drugs that are substrates of CYP2B6 may decrease when co-administered with Truqap (e.g., bupropion).

Substrates of UGT1A1

Concentration of drugs that are sensitive substrates of UGT1A1 may increase when co-administered with Truqap. Dose adjustment may be needed for drugs that are sensitive substrates of UGT1A1 (e.g., bictegravir, irinotecan).

Interactions with hepatic transporters (OATP1B1, OATP1B3)

The exposure of drugs that are sensitive to inhibition of 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 drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3 (e.g., simvastatin), if they are metabolised by CYP3A4. Refer to specific guidance in the prescribing information for these drugs.

Interactions with renal transporters (MATE1, MATE2K, OCT2)

The exposure of drugs that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by co-administration with Truqap. This may lead to increased toxicity. Transient serum creatinine increases may be observed during treatment with Truqap. due to inhibition of OCT2, MATE1 and MATE2K by capivasertib. Depending on their therapeutic window, dose adjustment may be needed for drugs that are sensitive to inhibition of MATE1, MATE2K, OCT2 (e.g., dofetilide, procainamide). Refer to specific guidance in the prescribing information for these drugs.

In vitro studies

Capivasertib inhibited CYP2C9, CYP2D6, CYP3A4 and UGT1A1 metabolizing enzymes and OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K drug transporters in *in vitro* studies.

Based on *in vitro* and physiologically based modelling, capivasertib was predicted to have no effect on the AUC of CYP2C9 or CYP2D6 substrates, atorvastatin or rosuvastatin. No meaningful interaction was predicted for metformin (2% to 40% AUC increase, depending on the dosing day).

4.6 Fertility, pregnancy and lactation

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, and re-testing 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 after the last dose for women and 16 weeks after the last dose for men.

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, 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).

Truqap is given with fulvestrant. Please refer to section 4.6 of the Summary of Product Characteristics (SmPC) 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 using machinery.

4.8 Undesirable effects

Summary of safety profile

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

The most common adverse reactions (reported at a frequency of ≥ 20%), were diarrhoea (72.4%), cutaneous adverse drug reactions (46.5%), nausea (34.6%), fatigue (34.6%), and vomiting (20.6%).

The most common grade 3 or 4 adverse reactions (reported at frequency ≥ 2%) were cutaneous adverse drug reactions (14.9%), diarrhoea (9.3%), hyperglycaemia (2.5%), hypokalaemia (2.3%), anaemia (2.0%), and stomatitis (2.0%).

Serious adverse reactions were seen in 26 (7.3%) patients receiving Truqap plus fulvestrant. Serious adverse reactions reported in ≥ 1% of patients receiving Truqap plus fulvestrant included cutaneous adverse drug reactions in 12 (3.4%), diarrhoea in 6 (1.7%), hyperglycaemia in 4 (1.1%) to include diabetic metabolic decompensation in 1 (0.3%), and vomiting in 4 (1.1%) patients.

Dose reductions due to adverse reactions were reported in 64 (18%) patients. The most common adverse reactions (reported at frequency ≥ 2%) leading to dose reduction of Truqap were diarrhoea (7.9%) and cutaneous adverse drug reactions (5.9%).

Treatment discontinuation due to adverse reactions occurred in 36 (10.1%) patients. The most common adverse reactions (reported at frequency ≥ 2%) leading to treatment discontinuation were cutaneous adverse drug reactions (5.4%), diarrhoea (2.0%), and vomiting (2.0%).

Tabulated list of adverse reactions

Adverse drug reactions 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 8 Adverse Drug Reactions observed in CAPItello-291 study

MedDRA SOC	MedDRA Term	Any Grade (%)	Grade 3 or 4 (%)
Infections and infestations	Urinary Tract Infection[1]	Very Common 49 (13.8)	6 (1.7)
Blood and lymphatic system disorders	Anaemia	Very Common 37 (10.4)	7 (2.0)
Immune system disorders	Hypersensitivity[2]	Common 4 (1.1)	1 (0.3)
Metabolism and nutrition disorders	Hyperglycaemia[3]	Very Common 63 (17.7)	9 (2.5)

MedDRA SOC	MedDRA Term	Any Grade (%)	Grade 3 or 4 (%)
	Decreased appetite	Very Common 59 (16.6)	1 (0.3)
	Hypokalaemia[4]	Common 16 (4.5)	8 (2.3)
	Diabetic Ketoacidosis[5]	Uncommon 1 (0.3)	1 (0.3)
Nervous system disorders	Dysgeusia	Common 21 (5.9)	0
Gastrointestinal disorders	Diarrhoea[6]	Very Common 257 (72.4)	33 (9.3)
	Nausea	Very Common 123 (34.6)	3 (0.8)
	Vomiting	Very Common 73 (20.6)	6 (1.7)
	Stomatitis[7]	Very Common 61 (17.2)	7 (2.0)
	Dyspepsia	Common 18 (5.1)	0
Skin and subcutaneous tissue disorders	Cutaneous adverse drug reactions[8]	Very Common 165 (46.5)	53 (14.9)
	Pruritus	Very Common 44 (12.4)	2 (0.6)
	Dry skin	Common 25 (7.0)	0
General disorders and administration site conditions	Fatigue[9]	Very Common 123 (34.6)	6 (1.7)
	Pyrexia[10]	Common 34 (9.6)	2 (0.6)
	Mucosal inflammation	Common 11 (3.1)	1 (0.3)
Investigations	Blood creatinine increased	Common	1 (0.3)

MedDRA SOC	MedDRA Term	Any Grade (%)	Grade 3 or 4 (%)
		16 (4.5)	
	Weight decreased	Common 12 (3.4)	0
	Glycosylated haemoglobin increased	Common 5 (1.4)	0

[1] Urinary Tract Infection includes urinary tract infection, pyuria, and cystitis.
[2] Hypersensitivity includes hypersensitivity, drug hypersensitivity and anaphylactic reaction.
[3] Hyperglycaemia includes hyperglycaemia, blood glucose increased, diabetes mellitus, type 2 diabetes mellitus and diabetic metabolic decompensation.
[4] Hypokalaemia includes blood potassium decreased and hypokalaemia.
[5] Diabetic Ketoacidosis includes ketoacidosis.
[6] Diarrhoea includes diarrhoea and frequent bowel movements.
[7] Stomatitis includes stomatitis, aphthous ulcer and mouth ulceration.
[8] Cutaneous adverse drug reactions include butterfly rash, dermatitis, dermatitis exfoliative generalised, drug eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema, erythema multiforme, papule, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, skin reaction, toxic skin eruption.
[9] Fatigue includes asthenia, fatigue and malaise.
[10] Pyrexia includes body temperature increased and pyrexia.

Description of selected adverse reactions (see section 4.4)

Hyperglycaemia

Hyperglycaemia of any grade occurred in 63 (17.7%) patients and grade 3 or 4 occurred in 9 (2.5%) patients receiving Truqap. In the 63 patients with hyperglycaemia, 30 (47.6%) patients were treated using anti-hyperglycaemic medication including metformin (30.1%) and insulin (17.4%). Out of the 63 patients with hyperglycaemia, dose reduction was required in 2 (3.1%) patients, dose interruption was required in 11 (17.4%) patients, and 1 (1.5%) patient discontinued treatment due to hyperglycaemia.

Diarrhoea

Diarrhoea occurred in 257 (72.4%) patients receiving Truqap. Grade 3 or 4 diarrhoea occurred in 33 (9.3%) patients. The median time to first occurrence was 8 days (1 to 519). In the 257 patients with diarrhoea, anti-diarrheal medication was required in 59% (151/257) of patients to manage diarrhoea symptoms. Out of 257 with diarrhoea, dose reduction was required in 28 (10.9%) patients, dose interruption was required in 35 (13.6%) and 7 (2.7%) patients discontinued Truqap due to diarrhoea. There was a higher incidence of diarrhoea in patients who were on metformin (88.6%) in comparison to that in patients who did not receive metformin in the study (70.1%).

Rash and other cutaneous adverse drug reactions

Cutaneous adverse drug reactions were reported in 165 (46.5%) patients. The median time to first occurrence was 12 days (1-377). Grade 3 or 4 occurred in 53 (14.9%) of patients who received capivasertib. Among the 165 patients with cutaneous adverse drug reactions, 44.8% (74/165) were treated with topical corticosteroids and 21.2% (35/165) with systemic corticosteroids. Out of 165 patients with cutaneous adverse drug reactions, dose reduction was required in 21 (12.7%) patients, dose interruption was required in 51 (30.9%) patients and 19 (11.5%) patients discontinued Truqap due to cutaneous adverse drug reactions.

Elderly

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

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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 AKT, loss of Phosphatase and Tensin Homolog (PTEN) function and mutations in the catalytic subunit of PI3K (PIK3CA).

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

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

Cardiac Electrophysiology

Based on an exposure-response 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

CAPItello-291 was a randomised, double-blind, placebo-controlled study that enrolled 708 patients, designed to demonstrate the efficacy and safety of Truqap in combination with fulvestrant in adult females, pre- or post-menopausal, and adult males with locally advanced (inoperable) or metastatic HR positive and HER2 negative breast cancer of whom 289 patients had tumours 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. Peri/pre-menopausal women were treated with an LHRH agonist. Randomisation was stratified by presence of liver metastases, prior treatment with CDK4/6 inhibitors and geographical region (region 1: US, Canada, Western Europe, Australia, and Israel vs region 2: Latin America, Eastern Europe, and Russia vs Region 3: Asia). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. A tumour sample was collected prior to randomisation to determine *PIK3CA/AKT1/PTEN* alteration status retrospectively by central testing.

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

The dual primary endpoints were investigator assessed progression free survival (PFS) in the overall population and PFS in the *PIK3CA/AKT1/PTEN*-altered subgroup per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

The key secondary endpoints of overall survival (OS) and objective response rate (ORR) will be formally analysed at future data cut offs.

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

The study demonstrated statistically significant 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 analysis of PFS in the 313 (44%) patients whose tumours 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 tumours have a *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.

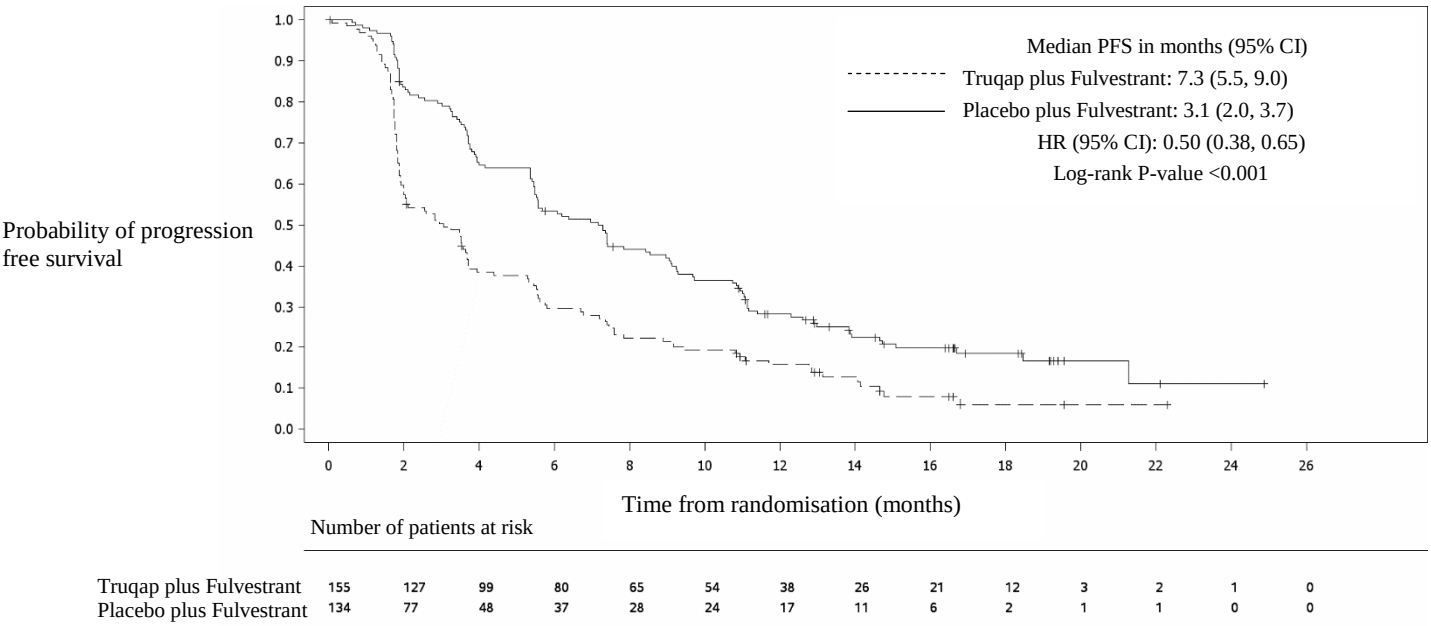
Table 9 Progression-free survival, by investigator assessment in the *PIK3CA/AKT1/PTEN*- altered subgroup

	***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 characterized in healthy subjects and patients with solid tumours. The systemic exposure (AUC and C_{max}) increased approximately proportionally over the dose range of 80 to 800 mg 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.

Biotransformation

Capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. The major metabolite in human plasma was an ether glucuronide that accounted for 78.4% of total drug-related material. Capivasertib accounted for 9.2% 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. 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 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.

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 human (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.

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

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

Tablet core
Microcrystalline cellulose
Calcium hydrogen phosphate
Croscarmellose sodium
Magnesium stearate

Tablet coating
Hypromellose
Titanium dioxide (E171)
Macrogols
Polydextrose

Copovidone
Triglycerides, medium chain
Iron oxide, black (E172)
Iron oxide, red (E172)
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack size:
64 tablets, comprising four Alu/Alu blisters of 16 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,

1 Francis Crick Avenue,

Cambridge,

CB2 0AA,

UK.

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 17901/0373

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/07/2024

10 DATE OF REVISION OF THE TEXT

07/05/2026