ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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.

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 CE-marked IVD with the corresponding intended purpose. If the CE-marked 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.

CTCAE Grade[a]	Recommendations
	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% (28.6% of patients) than those with a baseline HbA1C < 6.5% (15.4%). 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*.

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>
</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]
[*] 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 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 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 (16.9%), 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 6.8% 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 9.6% 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

MedDRA SOC	MedDRA term	Any grade (%)
Blood and lymphatic system disorders	Anaemia	Very common
Immune system disorders	Hypersensitivity[2]	Common
Metabolism and nutrition disorders	Hyperglycaemia[2]	Very common
	Decreased appetite	Very common
	Hypokalaemia	Common
	Diabetic ketoacidosis[3]	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
	Stomatitis[4]	Very common
	Dyspepsia	Common
Skin and subcutaneous tissue disorders	Rash[5]	Very common
	Pruritis	Very common
	Dry skin	Common
	Erythema multiforme	Common
	Drug eruption	Uncommon
	Dermatitis	Uncommon

MedDRA SOC	MedDRA term	Any grade (%)
	Dermatitis exfoliative generalised	Uncommon
	Toxic skin eruption	Uncommon
General disorders and administration site conditions	Fatigue[6]	Very common
	Mucosal inflammation	Common
	Pyrexia	Common
Investigations	Blood creatinine increased	Common
	Glycosylated haemoglobin increased	Common

[1] Urinary tract infection includes urinary tract infection and cystitis.
[2] Includes other related terms.
[3] Diabetic ketoacidosis includes ketoacidosis.
[4] Stomatitis includes stomatitis, aphthous ulcer and mouth ulceration.
[5] Rash includes erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.
[6] Fatigue includes fatigue and asthenia.

Description of selected adverse reactions

Hyperglycaemia
Hyperglycaemia of any grade occurred in 60 (16.9%) patients and grade 3 or 4 occurred in 8 (2.3%) patients receiving TRUQAP. 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 60 patients with hyperglycaemia, 28 (46.7%) patients were treated using anti-hyperglycaemic medication (including insulin in 16.7%). 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 listed in Appendix V.

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.

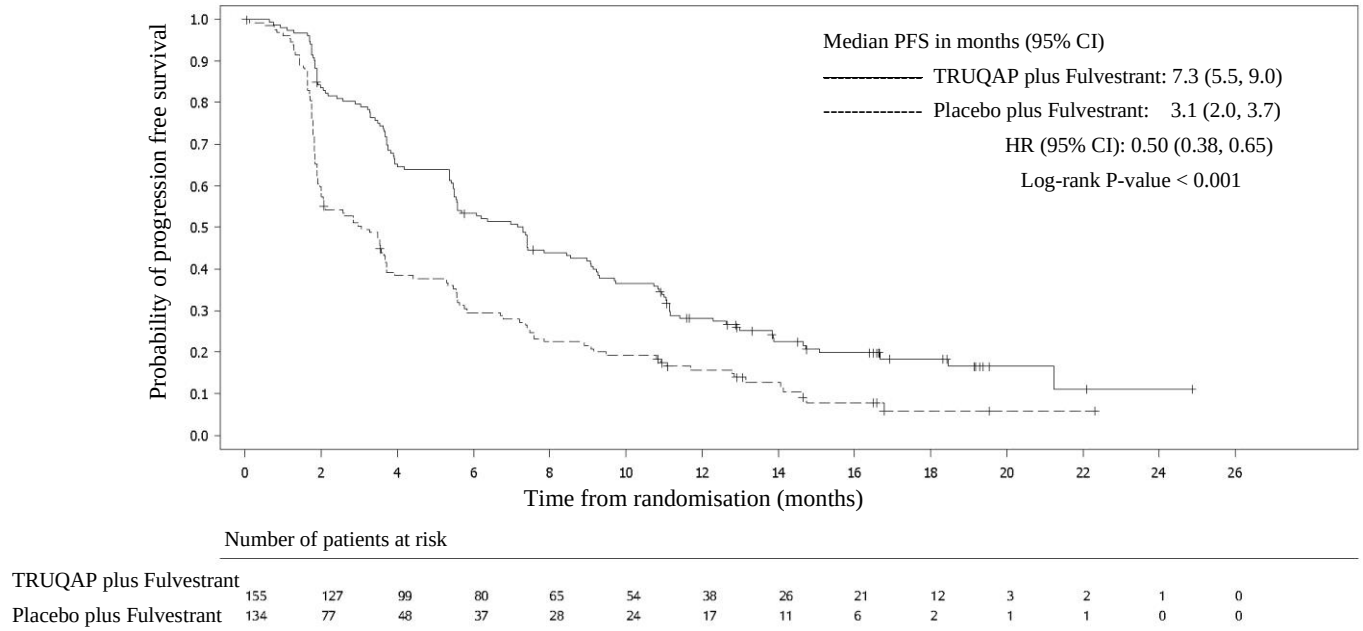
Table 9 Progression-free survival, by investigator assessment in *PIK3CA/AKT1/PTEN*-altered subgroup

	***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)



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with TRUQAP in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

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). 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.

Carcinogenicity studies have not been conducted with capivasertib.

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

4 years.

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

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. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1820/001 160 mg tablets
EU/1/24/1820/002 200 mg tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 June 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TRUQAP 160 mg film-coated tablets
capivasertib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 160 mg of capivasertib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

64 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

Record starting day here:

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1820/001 160 mg tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

truqap 160 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TRUQAP 200 mg film-coated tablets
capivasertib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of capivasertib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

64 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

Record starting day here:

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1820/002 200 mg tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

truqap 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

TRUQAP 160 mg tablets
capivasertib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Day 1
Day 2
Day 3
Day 4

Sun/moon symbols

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

TRUQAP 200 mg tablets
capivasertib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Day 1
Day 2
Day 3
Day 4

Sun/moon symbols

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TRUQAP is and what it is used for

What TRUQAP is

TRUQAP is a medicine used to treat cancer. It contains the active substance capivasertib. Capivasertib belongs to a group of medicines called AKT inhibitors.

What TRUQAP is used for

TRUQAP is used in combination with fulvestrant (another cancer medicine) to treat adult patients who have oestrogen receptor (ER) positive, HER2 negative breast cancer that is advanced or that has spread to other parts of the body with one or more abnormal "*PIK3CA", "AKT1", or "PTEN"* gene and whose cancer is not responding to other medicines that block the action of hormones (hormone therapy). Women who have not reached menopause will also be treated with a medicine called a luteinising hormone releasing hormone (LHRH) agonist. For men, your doctor will decide if you should be treated with LHRH agonist.

Your healthcare provider will test your cancer to see if it has at least one abnormal *"PIK3CA"*, *"AKT1"*, or *"PTEN"* gene to make sure that TRUQAP is right for you.

How TRUQAP works

TRUQAP works by blocking the effects of proteins called AKT kinases. These proteins help cancer cells to grow and multiply. By blocking their action, TRUQAP can reduce growth of the cancer cells. If you have any questions about how TRUQAP works or why this medicine has been prescribed for you, ask your doctor.

What other medicine TRUQAP is given with

When you take this medicine, you will also be given another medicine called fulvestrant.

2. What you need to know before you take TRUQAP

Do not take TRUQAP if:

You are allergic to capivasertib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Before you take TRUQAP, tell your healthcare provider if:

- You have or have ever had diabetes or high blood sugar (hyperglycaemia) or signs of high blood sugar including being very thirsty, having a dry mouth, needing to pass urine more often than usual, passing more urine than usual, having an increased appetite with weight loss.
- You have any current infections.
- You have diarrhoea or loose stools.
- You have a rash or other skin disorders.
- You have kidney problems or high levels of creatinine or uric acid in your blood (seen in blood tests).
- You have liver problems.

Ask your doctor to provide you with the package leaflet for fulvestrant as this contains important information about the medicine.

During your treatment with TRUQAP talk to your doctor immediately if you experience the following side effects. Your doctor may need to treat these symptoms, temporarily pause your treatment, reduce your dose, or permanently stop your treatment with TRUQAP:

<u>High blood sugar levels (hyperglycaemia)</u>

- Your doctor will monitor your blood sugar levels before you start the treatment with TRUQAP but also regularly during treatment with TRUQAP and more frequently in the first eight weeks of the treatment. Your blood sugar levels should be monitored on days 3 or 4 of the dosing week, before you take TRUQAP. Based on the results, your doctor will take any necessary actions, such as prescribing a medicine to lower blood sugar levels and seeking advice from a diabetologist. Your blood sugar levels and medication will need to be monitored more frequently if you have diabetes.
- Your doctor will tell you exactly when and where to have the blood tests. Treatment with TRUQAP may only be started if tests show that you have the right levels of sugar in your blood. This is because TRUQAP can increase sugar in your blood (hyperglycaemia) which could be serious and cause complications with fatal outcome.
- Signs of high blood sugar include being very thirsty, having dry mouth, needing to pass urine more often than usual, passing more urine than usual, having an increased appetite with weight loss. Additional symptoms such as nausea, vomiting, abdominal pain, difficulty breathing, fruity odour on breath, confusion, unusual fatigue, or sleepiness may be signs of an acute complication of increased blood sugar.

<u>Any signs of diarrhoea</u>

- Your doctor or pharmacist will advise you to drink more fluids or take medicines to treat diarrhoea.
- Signs of diarrhoea are loose or watery stools.

<u>Rash and other skin drug reactions</u>

- Signs of a rash and other skin drug reactions include rash, reddening of the skin, blistering of the lips, eyes or mouth, skin peeling, dry skin, skin inflammation with rash, shedding and/or scaling of skin surface.

Children and adolescents
TRUQAP is not recommended for children or adolescents under 18 years of age. The safety of TRUQAP and how effective it is has not been studied in this age group.

Other medicines and TRUQAP
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. Some medicines used to treat infection may increase the risk of side effects of TRUQAP and your doctor may need to reduce the dose of TRUQAP. See examples below:

- Certain antibiotics (e.g. clarithromycin, telithromycin).
- Certain antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole).
- Certain antivirals (e.g. boceprevir, nelfinavir, ritonavir, telaprevir).

Some medicines may reduce the effectiveness of TRUQAP, for example carbamazepine, phenytoin, St. John's Wort (a herbal medicine), and rifampicin.

TRUQAP may also increase the risk of side effects or alter the efficacy with certain other medicines such as bupropion, carbamazepine, cyclosporine, fentanyl, irinotecan, simvastatin. The doctor may need to adjust the dose of these medicines.

The medicines listed here may not be the only ones that could interact with TRUQAP.Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

Pregnancy and fertility
Do not take TRUQAP if you are pregnant or plan to become pregnant. TRUQAP may harm your unborn baby.
If you are a woman who could become pregnant, your doctor will ask you to provide a negative pregnancy test before starting treatment and advise you to perform a pregnancy test during your treatment.

Contraception for men and women
If you are a woman, you should avoid becoming pregnant while taking TRUQAP. Discuss contraception with your doctor if there is any possibility that you may become pregnant. If you are able to become pregnant, you should use effective birth control during treatment with TRUQAP and for 4 weeks after the last dose. If you do become pregnant during treatment, tell your doctor right away. Your doctor can advise you on suitable methods of contraception.

If you are a man, you must use a condom when having sexual intercourse with a female partner who is pregnant or able to become pregnant while you are taking TRUQAP and for 16 weeks after the last dose. Your female partner must also use a suitable method of contraception. You must tell your doctor if your female partner becomes pregnant.

Breast-feeding
Before taking TRUQAP, tell your doctor if you are breast-feeding. For the safety of your baby, you should not breast-feed during the treatment with TRUQAP.

Driving and using machines
TRUQAP may affect your ability to drive or use machines. If you feel tired while taking TRUQAP, take special care when driving or using tools or machines.

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

3. How to take TRUQAP

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- The usual starting dose is 400 mg (two 200 mg tablets) taken twice a day (a total of 4 tablets each day) for four days followed by three days of no dose. See Table 1.
- Swallow the tablets whole with water and take them 12 hours apart (2 in the morning and 2 in the evening) at about the same time of day on the dosing days.
- Do not chew, crush or split them before swallowing. Do not swallow any tablet that is broken, cracked or otherwise damaged as you may not be taking the full dose.
- You can take the tablets with or without food.

Table 1 TRUQAP dosing schedule

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.

Record the day you take your first dose on the carton.
While you take TRUQAP, you will also receive another medicine called fulvestrant. Your doctor will determine the dose and the schedule for fulvestrant.

If you vomit, do not take an additional dose. Take the next dose of TRUQAP at your usual time.
Avoid grapefruit and grapefruit juice while you are taking TRUQAP as it may increase the side effects of TRUQAP.

Depending on how your body responds to the treatment with TRUQAP, your doctor may adjust your TRUQAP dose. It is very important to follow your doctor's instructions. If you have certain side effects, your doctor may lower your dose, pause your treatment for a time, or stop your treatment.

The number of tablets to take depends on the dose prescribed as below:
- 400 mg dose: two 200 mg tablets twice daily
- 320 mg dose: two 160 mg tablets twice daily
- 200 mg dose: one 200 mg tablet twice daily

How long to take TRUQAP
Take TRUQAP for as long as your doctor tells you to.

This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is working as expected. If you have questions about how long to take TRUQAP, talk to your doctor or to your pharmacist.

If you take more TRUQAP than you should
If you take too many tablets, or if someone else takes your medicine, contact a doctor or hospital for advice immediately. Show the TRUQAP packet and this leaflet. Medical treatment may be necessary.

If you forget to take TRUQAP
If you miss a dose, you can still take it within 4 hours from the time you usually take it.

If it has been more than 4 hours after you usually take your dose, skip that dose. Take the next dose at your usual time. Refer to table 1 for dosing schedule. Do not take two doses to make up for a missed dose.

If you stop taking TRUQAP
Do not stop taking TRUQAP unless your doctor tells you to. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Immediately talk to your doctor if you experience the following side effects during treatment with TRUQAP. Your doctor may need to treat these symptoms, temporarily pause your treatment, reduce your dose, or permanently stop your treatment with TRUQAP.

High blood sugar levels (hyperglycaemia)
- Excessive thirst and dry mouth
- Needing to pass urine more often than usual
- Producing greater amounts of urine than usual
- Increased appetite with weight loss

Your doctor or pharmacist will monitor your blood sugar levels before you start and during treatment with TRUQAP. They will monitor your blood sugar levels more frequently if you have diabetes.

Diarrhoea
- loose or watery stool

Your doctor or pharmacist will advise you to drink more fluids or take medicine to treat diarrhoea.

Rash and other skin drug reactions
- Rash
- Reddening of the skin
- Blistering of the lips, eyes or mouth
- Skin peeling
- Dry skin
- Skin inflammation with rash
- Shedding and/or scaling of skin surface

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- Infection of the parts of the body that collect and pass out urine (urinary tract infection)
- Low level of haemoglobin in blood
- Loss of appetite
- Feeling sick (nausea)
- Vomiting
- Mouth sores or ulcers with gum inflammation (stomatitis)
- Itching (pruritus)
- Tiredness
- Headache

Common (may affect up to 1 in 10 people)
- Strange taste in the mouth (dysgeusia)
- Upset stomach, indigestion (dyspepsia)
- Skin eruptions
- Pain, redness and swelling of mucosa in different parts of the body, e.g. of genital mucosa (mucosal inflammation)
- High blood level of creatinine seen in blood tests, which may be a sign of kidney problems.
- High blood level of glycosylated haemoglobin (a marker of blood sugar level over the last 8 to 12 weeks)
- Reduced level of potassium in the blood
- Dizziness
- Syncope (fainting)

- Stomach pain
- Fever
- Kidney problems including rapid loss of kidney function (acute kidney injury)

Uncommon (may affect up to 1 in 100 people)
- Hypersensitivity
- Toxic skin eruptions (allergic rash)
- Diabetic ketoacidosis (a serious complication of high blood sugar level)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TRUQAP

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice any damage to the packaging or if the tablet is broken, cracked, or otherwise not intact.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TRUQAP contains
The active substance of TRUQAP is capivasertib.
- Each 160 mg TRUQAP film-coated tablet contains 160 mg capivasertib.
- Each 200 mg TRUQAP film-coated tablet contains 200 mg capivasertib.

The other excipients are:
- Tablet core: microcrystalline cellulose (E460i), calcium hydrogen phosphate, croscarmellose sodium (E468) and magnesium stearate (E470b) (see section 2 'TRUQAP contains sodium').
- Film-coating: hypromellose, titanium dioxide (E171), macrogol 3350, polydextrose, copovidone, medium chain triglycerides, black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172).

What TRUQAP looks like and contents of the pack
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).

TRUQAP is supplied in aluminium blisters (with symbols of sun for the morning/moon for the evening) containing 16 film-coated tablets. Each pack contains 64 tablets (4 blisters).

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
AstraZeneca S.A./N.V.
Tel: +32 2 370 48 11

България
АстраЗенека България ЕООД
Тел.: +359 24455000

Česká republika
AstraZeneca Czech Republic s.r.o.
Tel: +420 222 807 111

Danmark
AstraZeneca A/S
Tlf.: +45 43 66 64 62

Deutschland
AstraZeneca GmbH
Tel: +49 40 809034100

Eesti
AstraZeneca
Tel: +372 6549 600

Ελλάδα
AstraZeneca A.E.
Τηλ: +30 210 6871500

España
AstraZeneca Farmacéutica Spain, S.A.
Tel: +34 91 301 91 00

France
AstraZeneca
Tél: +33 1 41 29 40 00

Hrvatska
AstraZeneca d.o.o.
Tel: +385 1 4628 000

Lietuva
UAB AstraZeneca Lietuva
Tel: +370 5 2660550

Luxembourg/Luxemburg
AstraZeneca S.A./N.V.
Tél/Tel: +32 2 370 48 11

Magyarország
AstraZeneca Kft.
Tel.: +36 1 883 6500

Malta
Associated Drug Co. Ltd
Tel: +356 2277 8000

Nederland
AstraZeneca BV
Tel: +31 85 808 9900

Norge
AstraZeneca AS
Tlf: +47 21 00 64 00

Österreich
AstraZeneca Österreich GmbH
Tel: +43 1 711 31 0

Polska
AstraZeneca Pharma Poland Sp. z o.o.
Tel.: +48 22 245 73 00

Portugal
AstraZeneca Produtos Farmacêuticos, Lda.
Tel: +351 21 434 61 00

România
AstraZeneca Pharma SRL
Tel: +40 21 317 60 41

Ireland
AstraZeneca Pharmaceuticals (Ireland) DAC
Tel: +353 1609 7100

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
AstraZeneca S.p.A.
Tel: +39 02 00704500

Κύπρος
Αλέκτωρ Φαρμακευτική Λτδ
Τηλ: +357 22490305

Latvija
SIA AstraZeneca Latvija
Tel: +371 67377100

Slovenija
AstraZeneca UK Limited
Tel: +386 1 51 35 600

Slovenská republika
AstraZeneca AB, o.z.
Tel: +421 2 5737 7777

Suomi/Finland
AstraZeneca Oy
Puh/Tel: +358 10 23 010

Sverige
AstraZeneca AB
Tel: +46 8 553 26 000

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu