swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Truqap

International non-proprietary name: capivasertib
Pharmaceutical form: tablets
Dosage strength(s): 200 mg, 160 mg
Route(s) of administration: oral
Marketing authorisation holder: AstraZeneca AG
Marketing authorisation no.: 69300
Decision and decision date: approved on 19 March 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for capivasertib in the above-mentioned medicinal product.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Capivasertib is indicated in combination with fulvestrant for the treatment of adult patients with HR-positive HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine-based regimen.

2.2.2 Approved indication

Truqap is indicated in combination with fulvestrant for the treatment of adult female patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine-based regimen (see "Properties/Effects").

2.2.3 Requested dosage

The proposed dosage for capivasertib in combination with fulvestrant is 400 mg twice daily for 4 days on, followed by 3 days off.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	25 April 2023
Formal control completed	1 May 2023
Preliminary decision	15 November 2023
Response to preliminary decision	14 January 2024
Final decision	19 March 2024
Decision	approval

3 Medical context

Worldwide, breast cancer is the leading cause of cancer mortality in women[1]. Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer is the most frequent subtype of breast cancer; approximately 70% of all breast cancers are HR+, HER2-[2]. Despite the numerous available treatment options, advanced breast cancer remains an incurable disease. There is an unmet medical need for treatment options improving survival outcomes with manageable toxicity in these patients.

[1] World Health Organization, International Agency for Research on Cancer, The Global Cancer Observatory (GLOBOCAN), Breast cancer factsheet 2020.

[2] Howlader N et al., US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status, Journal of the National Cancer Institute, 2014;106(5).

4 Quality aspects

4.1 Drug substance

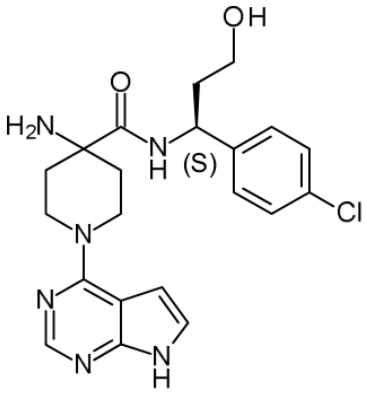
INN: Capivasertib

Chemical name: 4-amino-N-[(1S)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidinecarboxamide

Molecular formula: $C_{21}H_{25}ClN_6O_2$

Molecular mass: 428.92

Molecular structure:



Physico-chemical properties: Capivasertib is a white to off-crystalline white powder. It has one chiral centre and is manufactured as the S-enantiomer. Capivasertib demonstrates pH-dependent solubility. Only the desired, thermodynamically stable polymorphic form has been accessed through the drug substance manufacturing process. Capivasertib is non-hygroscopic.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is monitored with appropriate in-process controls and tests for isolated intermediates.

Specification: The structure of capivasertib has been elucidated using several spectroscopic techniques. To ensure a consistent quality, the specifications include the relevant test parameters as described in the current guidelines. Analytical methods have been described and validated according to ICH requirements.

Stability: The bulk drug substance is packaged in double PE bags and then placed in a rigid container. Appropriate stability data have been generated resulting in a suitable storage condition and retest period.

4.2 Drug product

Description and composition:

The drug product is an immediate release dosage form for oral administration. Capivasertib 160 mg tablets are beige, round, biconvex, film-coated tablets, approximately 10 mm in diameter. The tablets are marked with ‘CAV’ above ‘160’ on one side and plain on the reverse. Capivasertib 200 mg tablets are beige, capsule-shaped, biconvex, film-coated tablets, approximately 14.5 x 7.25 mm. The tablets are marked with ‘CAV200’ on one side and plain on the reverse. All excipients are widely used in pharmaceutical solid oral dosage forms. They meet the standards defined in the current Ph. Eur. with the exception of some components of the film coating which comply with European standards for food additives.

Pharmaceutical development:
Capsules were used in phase 1 clinical studies. Tablets were introduced for phase 2 clinical studies, and an improved tablet formulation was used in phase 3 clinical studies. The commercial formulation is the same as the phase 3 formulation.

Manufacture:
The drug product is manufactured in a standard manufacturing process, which includes mixing, compaction, milling, tableting, and film-coating steps. Process parameters and in-process controls are defined. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Specification:
For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life are established. The specifications include the parameters: description (visual); identity tests; assay (IR); degradation products (LC); dissolution; and uniformity of dosage units (Ph. Eur.). The analytical procedures are adequately described, and non-compendial methods are validated according to the current ICH requirements. Batch analysis data have been provided. The results are within the specifications and are consistent from batch to batch.

Container closure system:
Satisfactory information on the proposed container closure system has been provided. The drug product is packaged in aluminium-aluminium blisters.

Stability:
Appropriate stability data have been generated following the relevant (ICH) guidelines. Based on the stability studies, appropriate shelf-life and storage conditions have been established.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Capivasertib inhibited AKT 1, 2 and 3 and also two other serine/threonine kinase (P70S6K and PKA) with IC_{50} values in low nanomolar range in biochemical enzyme assays.

Capivasertib showed anti-proliferative activity in different cell lines, including cell lines derived from breast cancers, at half growth inhibition concentration (GI_{50}) less than 1 µM, irrespective of the presence of mutations in PIK3CA, PTEN and AKT1. The combination of capivasertib (500 nM) and fulvestrant (1 nM) significantly reduced proliferation of the naive and ER+ breast cancer cell lines when compared with each monotherapy. The major human metabolite (M2) had no cellular activity at concentrations up to 30 µM.

In mouse xenograft models, capivasertib below 100 mg/kg, inhibited time- and dose-dependently the phosphorylation of AKT substrates in tumours, with 50% inhibition of PRAS40 phosphorylation occurring at a plasma drug concentration of ~ 0.1 µM.

Dosing capivasertib in combination with fulvestrant (5 mg/animal) resulted in a significant improved treatment response compared with monotherapy.

Secondary pharmacology investigations showed that capivasertib at 10 µM inhibited significantly ROCK1 with a IC_{50} in the same range of human C_{max} at steady state. Capivasertib, however, was approx. 50-fold more efficient in blocking the phosphorylation of AKT-substrate when compared to phosphorylation of ROCK's substrate, in cellular assays, including ER+ breast cancer models with and without mutations in PIK3CA.

Safety pharmacology studies were performed according to ICH S7A and 7B. In a modified Irwin screen in conscious rats, reduction in spontaneous activity and touch response were noted at an exposure lower than the human exposure at therapeutic dose. In conscious telemetered beagle dogs, decreased heart rate, QT and QTc interval prolongation, and an increase in LVdP/dt+ (index of cardiac contractility) occurred at ≥30 mg/kg, along with elevation of glucose and insulin levels. The NOAEL was 5 mg/kg. In the 1-month repeat-dose study at 30 mg/kg/day in dogs, QTc interval was prolonged but normalised within the 1-month recovery period. In addition, an increase of ejection and a moderate decrease of cardiac output were observed at exposure levels lower than human exposure at therapeutic dose. These effects were also observed in humans and are related to the pharmacological effect of capivasertib, as inhibition of the PI3K/AKT/mTOR pathway is implicated in regulating cardiac repolarisation and QTc prolongation.

No effects were observed on respiratory functions in male rats following a single oral dose. Gastric emptying in male rats was reduced at exposure levels lower than the human exposure levels at therapeutic dosing.

5.2 Pharmacokinetics

Capivasertib was rapidly absorbed in mice, rats, and dogs (T_{max} at 0.3-0.5 h in mice and rats, and up to 4 h in dogs). C_{max} generally increased dose-proportionally in all three species. AUC_{0-t} increased in a greater than dose proportional manner in mice and rats and dose-proportionally in dogs. No obvious sex-related differences were noted. In humans, capivasertib exposure (AUC and C_{max}) increased dose-proportionally after single dose administration.

Capivasertib bound in a similar extent to plasma proteins from mice, rats, dogs and humans. It preferentially distributed into blood cells. [^{14}C]-capivasertib showed a rapid distribution to the majority of tissues 1 h post-dose in rats. Half-lives for the declines in tissue radioactivity were between 2 and 10 hours in the majority of tissues. In pigmented rats, radioactivity was confined to pigmented skin and the uveal tract of the eye up to 168 h and 504 h, respectively.

In rat, dog and human hepatocytes, [^{14}C]-capivasertib was rapidly metabolised. All the metabolites generated by human hepatocytes were also formed by rat or dog hepatocytes. *In vivo*, unchanged capivasertib was the major circulating drug-related component (63% of total AUC) in rats. M2, the major human metabolite, is a glucuronide conjugate and therefore considered of no toxicological concern.

Faecal route was the main elimination route in nonclinical species, while both faecal and urinary routes were major routes of elimination in humans. Capivasertib was detected in the plasma of suckling rat pups, suggesting its transfer to milk. Placental transfer was not investigated.

5.3 Toxicology

Rats and dogs are considered appropriate for toxicological assessment, because of comparable metabolism and pharmacokinetic profiles to humans. The clinical oral route is used but the dosing regime was single daily dosing in contrast to intermittent dosing in humans.

In mice and rats, mortality/moribundity occurred at ≥300 mg/kg/day. The cause of death was not determined.

The key target systems identified in the repeat-dose toxicity studies were insulin signalling (mice, rats, dogs), renal function (rats, dogs), reproductive system in males (mice, rats, dogs), and heart function (dogs, see Pharmacology). Increased blood insulin and/or glucose levels were observed in all toxicological species. These changes are considered related to the pharmacology of capivasertib as hyperglycaemia is published to be one of the most common on-target adverse effects of PI3K/AKT inhibitors. In rats, renal effects, including increased urine output (polyuria), proteinuria and increased water consumption, as well as decreased tubular epithelial cell size associated with nuclear crowding were noted in the kidneys, which correlated with reduced kidney weight and size. These effects could also be due to the pharmacological function of capivasertib, as AKT signalling is known to play a role in proximal tubular glucose and phosphate transport. In addition, capivasertib inhibited renal tubular transporter proteins without any corresponding renal function impairment. Reproductive system of males was affected in all three nonclinical species, including lower mean epididymis and testis weights, which correlated with germ cell depletions. In the 1-month study in rats and dogs, there were irreversible pathological changes in the reproductive system of males at ≥30 mg/kg/day.

Capivasertib was not genotoxic *in vitro* but it was genotoxic with an aneugenic mode of action *in vivo*. In accordance with ICH S9 no carcinogenicity study is required for the proposed indication.

Based on the data derived from the repeat-dose studies, capivasertib treatment did not impair male fertility in rats. Female fertility was not studied in accordance with the ICH S9 guideline. In an embryofetal development study, the administration of capivasertib was associated with maternal toxicities and adverse developmental outcomes, including embryofetal deaths, reduced fetal weights, and fetal visceral variations at exposure levels that were lower than human exposure at therapeutic dosing. In the pre- and postnatal study, pregnant rats received capivasertib up to 150 mg/kg/day from gestation day 6 through lactation day 6. Administration of 150 mg/kg/day resulted in reduced litter and pup weights.

In knockout mice, the deletion of AKT1/2 results in fetal defects and postnatal growth abnormalities. Therefore, the abovementioned fetal effects are likely related to the pharmacological effects of capivasertib.

Juvenile toxicity studies have not been conducted as the patient population for this application are adult patients. Capivasertib did not demonstrate phototoxic potential *in vitro*.

The description of the safety findings from the nonclinical studies and their evaluation can be found in Module SII of the RMP, but some changes are suggested.

No significant risk for the environment is expected as a result of the introduction of capivasertib to the market.

5.4 Nonclinical conclusions

The pharmaco-toxicological profile of capivasertib has been sufficiently well characterised. The submitted nonclinical data support the approval of Truqap in the proposed indication. Toxic effects can largely be explained by the pharmacology of capivasertib. The relevant information has been included in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption and biopharmaceutical development
Three immediate release formulations were administered in the course of capivasertib development: the Phase 1 capsule, the Phase 2 tablet and the Phase 3/commercial tablet. Apart from debossing, the Phase 3 and the proposed commercial tablet are identical. The Phase 3 tablet was administered in the pivotal Phase 3 study CAPItello-291 (D3615C00001).

The absolute bioavailability of the Phase 3 tablet was 29%. The co-administration of the Phase 3 tablet with the PPI rabeprazole had no impact on capivasertib AUC and resulted in a 27% decrease of Cmax. Capivasertib median tmax increased from 1.5 h after fasted administration to 2.0 h after co-administration of rabeprazole. The administration of the Phase 3 tablet with a high-fat high-calorie meal caused a 23% and 32% increase of capivasertib Cmax and AUCinf, respectively. The median tmax was prolonged from 1.5 h to 2.26 h. These data support the administration of capivasertib independently of meals and PPI intake.

Dose proportionality
After single dose administration, capivasertib Cmax and AUC0-12h increased proportionally to administered doses between 80 mg and 640 mg. After multiple dosing, capivasertib Cmax,ss and AUC0-12h,ss increased approximately dose-proportionally after doses of 80 mg to 480 mg. At higher doses (640 mg), a more than dose proportional increase was estimated.

Pharmacokinetics after multiple dosing
After the proposed intermittent dosing of capivasertib 400 mg BD [4/3], steady-state was predicted to be attained on every 3rd and 4th dosing day each week, starting from week 2. The estimated accumulation ratio was 1.58.

Distribution
The *in vitro* plasma protein binding of capivasertib was approximately 80% and across a range of 0.05 to 5.0 µg/mL independent of the capivasertib concentration and comparable in male and female human plasma. Capivasertib binds to both human albumin (per cent bound: 70.5%) and α1-acid glycoprotein (per cent bound: 28.1%).

The capivasertib mean *in vitro* blood to plasma ratio was 0.714. This was in good agreement with the *ex vivo* measurements after administration of a ^{14}C-labelled capivasertib dose, where the blood to plasma ratios ranged from 0.65 to 0.85.

The capivasertib mean apparent volume of distribution at steady state in a typical patient was 322 L.

Metabolism and elimination

In vitro data
Approximately 44% of capivasertib *in vitro* clearance was mediated by CYPs (predominantly oxidation), and 53% predominantly by UGT with a minor contribution by SULT.

The UGTs involved in capivasertib *in vitro* metabolism were UGT1A1, UGT1A3, UGT1A4, UGT1A9 and UGT2B7, with UGT2B7 as the major enzyme involved in the formation of AZ14102143 (inactive main metabolite) contributing 84% of the total glucuronidation amongst the seven tested isoforms. Capivasertib was not a substrate of UGT1A6 and UGT2B15.

The CYPs involved in capivasertib *in vitro* metabolism were CYP2D6, CYP3A4, CYP3A5, CYP2C9, CYP1A1, CYP2C19, and CYP2B6 but not by CYP1A2, CYP2A6, CYP2C8, or CYP2E1, with CYP3A4 as the main contributor.

Clinical data
Exposure to capivasertib accounted for 9.1% of the total radioactivity in plasma based on AUC, indicating the presence of metabolites in plasma. Capivasertib plasma concentrations and the total radioactivity in plasma declined in parallel up to 24 h post-dose. The total radioactivity in plasma was no longer measurable (most likely due to the assay), resulting in a shorter half-life compared to capivasertib (5.4 h versus 12.3 h).

The most abundant compound in plasma was the inactive glucuronide metabolite AZ14102143 (M11), accounting for 78.4% of the AUC of the total radioactivity in plasma, followed by capivasertib (9.2%). Several other metabolites were detected in plasma, none of them accounting for more than 2% of the AUC of the total radioactivity in plasma. More than 90% of the total radioactivity in plasma was assigned to capivasertib and its metabolites. The abundance of AZ14102143 and capivasertib in plasma was similar in early (0-2 h) and late (4-24 h) post-dose samples.

In agreement with these results, the AUC of the glucuronide metabolite AZ14102143 was approximately 7- to 9-fold higher than the AUC of the parent compound capivasertib.

After oral administration of a ^{14}C-labelled dose, 44.7% and 50.4% of the dose was excreted in urine and faeces, respectively.

Within 168 h post-dose, 7.4% of the dose was excreted in urine as unchanged capivasertib after oral administration.

The most abundant compound excreted in urine was the inactive glucuronide metabolite AZ14102143 (M11), accounting for 28.2% of the administered radioactive dose, followed by capivasertib (7.1%). Several other metabolites were detected in urine, none of them accounting for more than 2% of the administered radioactive dose. More than 90% of the total radioactivity excreted in urine was assigned to capivasertib and its metabolites. The abundance of AZ14102143 and capivasertib excreted in urine was similar in early (0-12 h) and late (12-48 h) post-dose samples.

The most abundant compound excreted in faeces was capivasertib, accounting for 29% of the administered radioactive dose. AZ14102143 was not quantifiable in faeces. Several other metabolites were detected in faeces, none of them accounting for more than 2% of the administered radioactive dose. More than 70% of the total radioactivity excreted in faeces was assigned to capivasertib and its metabolites.

Following the proposed intermittent dosing of capivasertib 400 mg BD [4/3], the initial CL/F was estimated at 60.0 L/h. It decreased by 8% after 7 days. The effective half-life of capivasertib derived from the pop PK model was 8.34 h.

Special populations

No dedicated studies in special populations were conducted for capivasertib. Instead, the potential impact of demographic and other factors on the pharmacokinetics of capivasertib in cancer patients was investigated in a pop PK analysis.

The final dataset included 781 patients with advanced or metastatic solid tumours. The average age and body weight of these patients was 57 years (range 26 to 87 years) and 66 kg (range 32 to 150 kg), respectively. Most of the patients (73.8%) were younger than 65 years old. The dataset included 22.2% patients ≥ 65 years and < 75 years, and 4.1% patients ≥ 75 years old.

The majority (88.1% and 66.3%) of the patients were female and white. Most of them (64.7%) had normal hepatic function, 34.3% had mild hepatic impairment. The dataset included 7 (0.9%) patients with moderate hepatic impairment and no patients with severe hepatic impairment. Regarding renal function, it was normal in 54.3% of the patients. The dataset included 34.2% and 10.9% of patients with mild or moderate renal impairment, respectively. There were no patients with severe renal impairment in the dataset. The doses administered ranged from 80 mg to 800 mg, with most patients on 400 mg (62.6%) or 480 mg (22.4%).

The final model was a 3-compartment model with combined first and zero order absorption and time- and dose-dependent CL/F. The covariates evaluated included race, sex, hepatic function, dose, smoking, CYP3A inducers, CYP3A inhibitors, body weight, age, CRCL, renal function, eGFR, paclitaxel, fulvestrant and acid reducing agents. Of these, the final model included the following covariate relationships:

- Dose and paclitaxel as covariates of Imax
- Body weight as covariate of F1 and baseline clearance
- Age as covariate of baseline clearance

The model described the capivasertib concentrations for the initial 24 h post-dose reasonably well. It over-predicted the variability of the data at later sampling times.

Capivasertib steady state exposures decreased with increasing body weight and increased with increasing age. However, the changes were within 80% and 125% of the reference. This was the case for covariates not included in the final model (comedications, hepatic and renal function, race, sex, smoking status) as well.

The results of the pop PK analysis support the dosing recommendations for special populations from a pharmacokinetic point of view.

Interactions

Impact of other drugs on capivasertib

In vitro data
Capivasertib was mainly metabolised by CYP3A4 and UGT2B7 *in vitro*. Capivasertib was a substrate for P-gp and OCT2, but not for BCRP, OATP1B1 or OATP1B3.

Clinical data
After administration of a single 80 mg dose of capivasertib with multiple doses of itraconazole (strong CYP3A4 inhibitor), there was a 1.7-fold and 1.95-fold increase of capivasertib Cmax and AUCinf, respectively. The capivasertib half-life was slightly prolonged from 7.4 h to 10.3 h. The metabolite/parent ratio (AZ14102143) decreased from 8.8 to 5.8.

This was the only clinical interaction study with capivasertib as a victim. The impact of the following perpetrators on capivasertib exposures after the proposed therapeutic dosing scheme (400 mg BD, 4 days on, 3 days off) was investigated by PBPK modelling:

- CYP3A4 inhibitors: strong inhibitor, itraconazole; moderate inhibitors, erythromycin and verapamil; weak inhibitor, cimetidine

- Strong CYP3A4 inducer: rifampicin

- Weak or moderate CYP4A4 inducer: modafinil 200 mg or 400 mg QD

- UGT2B7 inhibitor: probenecid

The PBPK model was successfully validated with regard to the prediction of the capivasertib exposures under different conditions.

The PBPK simulations indicated the following changes of capivasertib AUC after therapeutic dosing:

- Itraconazole: 1.56-fold ↑ (1st on-dosing day)
- Erythromycin: 1.42-fold ↑ (1st on-dosing day)
- Verapamil: 1.41-fold ↑ (1st on-dosing day)
- Cimetidine: 1.05- fold ↑ (1st on-dosing day)
- Probenecid: 1.37-fold ↑ (1st on-dosing day)
- Rifampicin: 73% ↓ (1st on-dosing day)
- Modafinil 200 mg: 16% ↓ (1st on-dosing day)
- Modafinil 400 mg: 23% ↓ (1st on-dosing day)

The results of the clinical interaction study and the PBPK simulations support the dosing recommendations regarding the co-administration of capivasertib with strong or moderate CYP3A4 inhibitors or inducers.

Impact of capivasertib on other drugs

In vitro data

Capivasertib
The static interaction risk assessment based on the *in vitro* data indicated the following signals for an *in vivo* interaction:

- Reversible inhibition of CYP2C9, 2D6 and 3A4/5, with the lowest IC50/Ki for the inhibition of CYP2D6.

- Time-dependent inhibition of CYP3A4/5

- Induction of CYP3A4.

- Inhibition of intestinal BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K.

- Inhibition of UGT1A1 and 1A4.

AZ14102143
The glucuronide metabolite did not inhibit any of the CYPs investigated (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5) at concentrations up to 300 µM. An inhibition of OATP1B1 at therapeutic exposures could not be excluded, while the inhibition of P-gp or BCRP was unlikely.

Clinical data

After administration of the proposed therapeutic dose (400 mg BD, 4 days on, 3 days off), capivasertib caused a 1.12-fold and 1.15-fold increase of midazolam (CYP3A4 substrate) Cmax and AUCinf, respectively on Day 8 (last day of the first treatment week, i.e. on the third day off treatment). On Day 12 (fourth dosing day of the second week), midazolam Cmax and AUCinf showed a 1.24-fold and 1.77-fold increase. These were the only clinical interaction data of capivasertib as a perpetrator.

The PBPK model described above predicted the impact of capivasertib on midazolam exposures reasonably well. It was used to predict the impact of capivasertib at the proposed therapeutic dose on the following substrates:

- CYP2D6 probe substrate: desipramine
- UGT1A1 substrate: raltegravir
- OATP1B1 and OATP1B3 probe substrate: atorvastatin (which is also a substrate of CYP3A4)
- BCRP, OATP1B1, and OATP1B3 probe substrate: rosuvastatin
- MATE1, MATE2-K, and OCT2 probe substrate: metformin

The maximum predicted change of the substrates' exposures was a 1.4-fold increase of metformin AUC in the presence of capivasertib.

In addition to the main simulations, sensitivity analyses with 10-fold higher and 10-fold lower values of the relevant parameters were conducted. Apart from MATE1, the variations had no significant impact on the substrates' exposures.

The results of the clinical interaction study and the PBPK simulations supported the dosing recommendations regarding the co-administration of capivasertib and substrates of CYP3A4, OATP1B1, OATP1B3, MATE1, MATE2K, or OCT2. The uncertainties associated with PBPK simulations of interactions with transporters were taken into consideration for the respective dosing recommendations.

Pharmacodynamics

Secondary pharmacology (safety)

No dedicated tQT study was conducted with capivasertib. Instead, an exposure-response analysis including the data of Study D3610C00001 was provided. Matched PK and ECG measurements were available after single dose administration only, but a wide dose range of 80 mg to 800 mg was covered. As the proposed regimen of 400 mg BID 4/3 was not administered in Study D3610C00001, Cmax after continuous dosing of 400 mg BID was used as the reference value for therapeutic exposure in the ER analysis. It was comparable to the estimated Cmax after the proposed regimen. The highest mean Cmax included in the analysis was 2.8-fold higher than Cmax after the proposed therapeutic dosing regimen. The data of 180 patients were included in the analysis.

The use of single dose data was acceptable because capivasertib showed no major accumulation and the inactive glucuronide was its only major (inactive) metabolite. Limitations of the dataset were the lack of placebo data and the availability of only one predose ECG measurement.

There were no QTcF values ≥ 480 ms. QTcF values ≥ 450 ms were observed in 7 patients after 480 mg BID 4/3 and 1 patient after 640 mg BID 2/5. There were no QTcF prolongations ≥ 60 ms and 1 QTcF prolongation ≥ 30 ms after 640 mg BID 2/5.

There was a trend of PR and QRS shortening with increasing capivasertib concentrations. Capivasertib had no apparent effect on heart rate in the different dose groups. Considering the fact that only one predose assessment per patient was available, QTcF was the best correction for heart rate.

There was a statistically significant relationship between capivasertib plasma concentrations and ΔQTcF. The model described the mean data reasonably well, but not their variability. The predicted

ΔQTcF at the proposed therapeutic dosing regimen was 3.87 ms (90% CI: 2.77-4.97). At higher exposures, the upper limit of the 90% CI exceeded 10 ms.

In summary, at the proposed therapeutic dosing regimen a clinically relevant QTcF prolongation seems unlikely, but it cannot be excluded at higher exposures.

6.2 Dose finding and dose recommendation

Phase 1 clinical studies evaluated increasing doses of capivasertib monotherapy under continuous and intermittent dose schedules. Dose-limiting toxicities under continuous dose schedules were rash and diarrhoea. Based on the preliminary safety data, the recommended dose for further clinical evaluation was determined as capivasertib 480 mg twice-daily for 4 days followed by 3 days of treatment pause (4on/3off). Further evaluation of capivasertib monotherapy showed limited tumour responses but promising results in combination with fulvestrant. In Phase 2 clinical studies, combination therapy with capivasertib 400 mg twice-daily dose with intermittent (4on/3off) schedule was determined as suitable for further evaluation, whereas higher doses were regarded as not suitable for long-term dosing in combination with fulvestrant due to safety concerns. The latter dose was subsequently evaluated in the Phase 3 clinical study.

6.3 Efficacy

Study CAPItello-291 (D3615C00001) is an ongoing Phase 3 double-blind, placebo-controlled, 1:1 randomised clinical trial evaluating capivasertib combined with fulvestrant versus placebo combined with fulvestrant. The study included patients with HR+ HER- advanced breast cancer who have received treatment with an aromatase inhibitor-containing regimen (single agent or in combination) and had i) disease recurrence/progression while on, or within 12 months of the end of (neo)adjuvant treatment with an aromatase inhibitor, or had ii) disease progression while on aromatase inhibitor administered as a treatment line for advanced breast cancer. Furthermore, not more than 2 prior lines of endocrine therapy for advanced breast cancer and not more than 1 prior line of chemotherapy for advanced breast cancer were allowed. All study patients were required to have a tumour sample (from primary or recurrent disease diagnosis) for retrospective molecular testing of AKT-pathway alteration status. At least 51% of the overall study population were required to have received prior therapy with a CDK4/6 inhibitor. Patients were stratified by region, presence of liver metastases, and prior exposure to CDK4/6 inhibitor but not for AKT-pathway alterations. Further details on the study entry criteria are found in the section “Clinical Efficacy” of the attached information for healthcare professionals.

The dual primary endpoints are progression-free survival (PFS) per investigator assessment in the 1) overall study population and 2) patients with AKT pathway-altered tumours (PIK3CA, AKT1 or PTEN alteration). Overall survival (OS) in 1) overall population and 2) AKT pathway-altered tumours are key secondary endpoints included in the hierarchical testing procedure. Additional assessment by blinded independent review committee (BICR) was provided.

A total of 708 patients were randomised to receive treatment with capivasertib combined with fulvestrant (n = 355) or placebo combined with fulvestrant (n = 353). Of these, 155 in the capivasertib combined with fulvestrant arm and 134 in the placebo combined with fulvestrant arm had tumours with PIK3CA/AKT1/PTEN alterations. The demographic and baseline disease characteristics were balanced. For further details on the included study population please refer to the attached information for healthcare professionals, section “Clinical Efficacy”.

In the primary analysis of progression-free survival (data cut-off from August 2022), capivasertib combination therapy demonstrated statistically significant prolongation of investigator assessed

progression-free survival in the PIK3CA/AKT1/PTEN-altered population (HR 0.50 CI95% 0.38, 0.65, median PFS was 7.3 months in the experimental arm compared to 3.1 months in the placebo containing arm). An overall survival analysis was performed at data cut-off in August 2022. The overall survival results in overall and PIK3CA/AKT1/PTEN-altered population were immature. However, no early detriment was visible.

Furthermore, only a limited number of males received capivasertib in the pivotal study (n=3), of whom none had a PIK3CA/AKT1/PTEN alteration.

6.4 Safety

The most frequently reported toxicities that occurred in patients treated with capivasertib monotherapy and in combination with fulvestrant were: diarrhoea, nausea, rash, fatigue, vomiting, headache, decreased appetite, hyperglycaemia, and stomatitis. In the CAPItello-291 study, capivasertib combined with fulvestrant compared to fulvestrant combined with placebo resulted in a more than 2-fold increase of grade ≥3 treatment emergent adverse events (TEAEs, 43.7% in the experimental arm versus 16.6% in the control arm) and serious adverse events (17.5% vs 8.6%, respectively), and increase of TEAEs leading to discontinuation of either capivasertib or placebo (14.1% vs 2.3%, respectively). The following grade 5 adverse events were reported in the capivasertib combined with fulvestrant arm: aspiration pneumonia, sepsis, acute myocardial infarction, cerebral haemorrhage, and liver abscess. For further details regarding safety please refer to the attached information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

The pivotal study demonstrated statistically significant progression-free survival benefit for capivasertib combined with fulvestrant in the PIK3CA/AKT1/PTEN-altered study population. Overall survival data were immature. Addition of capivasertib to fulvestrant alone resulted in increased toxicity including grade ≥3 treatment emergent adverse events, serious adverse events, and fatal events. However, safety is manageable and adequately described in the information for healthcare professionals.

The benefit-risk assessment is positive for female HR+ HER2- advanced breast cancer patients with PIK3CA/AKT1/PTEN alterations who had disease recurrence or progression on or after prior endocrine-based therapy.

Regarding clinical pharmacology aspects, capivasertib can be taken independently of food intake and together with PPIs. The impact of demographic covariates on capivasertib exposures was small, i.e., from a pharmacokinetic point of view, no dose adjustments are required for special populations with sufficient representation in the pop PK analysis. Limited or no data were available for patients ≥ 75 years, patients with severe renal impairment and patients with moderate or severe hepatic impairment. Capivasertib is not likely to cause a QTc prolongation at therapeutic exposures. However, there was a positive correlation between capivasertib plasma concentrations and ΔQTcF, i.e., a clinically relevant impact on QTc cannot be excluded at supratherapeutic exposures.

Capivasertib is a substrate for CYP3A4 and UGT2B7. The co-administration with strong or moderate CYP3A4 inducers or strong CYP3A4 inhibitors should be avoided. Capivasertib inhibits CYP3A4, OATP1B1, OATP1B3, MATE1, MATE2K, and OCT2. Precautionary labelling for the respective substrates is required and implemented.

The clinical pharmacology data of capivasertib are sufficient. Its interaction potential and the missing data in some special population groups are addressed in the information for healthcare professionals.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Truqap was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Truqap®, film coated tablets

Composition

Active substances

Capivasertib

Excipients

Tablet core: Microcrystalline cellulose (E460), dibasic calcium phosphate, croscarmellose sodium (corresp. sodium max. 1,82 mg in 160 mg film coated tablets and max. 2,28 mg in 200 mg film coated tablets), magnesium stearate.

Tablet coating: Hypromellose, titanium dioxide (E 171), polyethylene glycol 3350, polydextrose (E 1200), copovidone (K-28), medium chain triglycerides, yellow iron oxide (E 172), red iron oxide (E 172), black iron oxide (E 172).

Pharmaceutical form and active substance quantity per unit

Truqap 160 mg tablets are round, biconvex, beige, film coated tablets debossed with ‘CAV’ above ‘160’ on one side and plain on the reverse.
Truqap 200 mg are capsule shaped, biconvex, beige film coated tablets debossed with ‘CAV 200’ on one side and plain on the reverse.
Film-coated tablets containing 160 mg respectively 200 mg capivasertib.

Indications/Uses

Truqap is indicated in combination with fulvestrant for the treatment of adult female patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN* alterations following recurrence or progression on or after an endocrine-based regimen (see “Properties/Effects”).

Dosage/Administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer. Patients with hormone receptor (HR) positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) advanced breast cancer should be selected for treatment with Truqap based on the presence of one or more PIK3CA/AKT1/PTEN mutations using a validated test.

Usual dosage

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

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

In pre/peri menopausal women, treated with the combination of Truqap with fulvestrant should receive a luteinizing hormone releasing hormone (LHRH) agonist according to current clinical practice standards.

Refer to the approved Prescribing Information of fulvestrant for more information.

If a dose of Truqap is missed, it can be taken within 4 hours after the time it is usually taken. After more than 4 hours, the dose should be skipped. The next dose of Truqap should be taken at the usual time. There should be at least 8 hours between doses. If the patient vomits, an additional dose should not be taken. The next dose of Truqap should be taken at the usual time.

Truqap should be continued until disease progression or unacceptable toxicity occurs.

Table 1: Truqap dosing schedule for each week

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5***	**Day 6***	**Day 7***
Morning	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			
Evening	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			

* No dosing on day 5, 6 and 7

Dose adjustment

For Adverse Reactions

Treatment with Truqap may be interrupted to manage adverse reactions and dose reduction can be considered. If dose reduction is considered, the dose reduction guidelines are described in Table 2. The dose of Truqap can be reduced up to two times. Permanently discontinue Truqap if unable to tolerate the treatment after the second dose reduction. 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

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

Consider a consultation with diabetologist/endocrinologist when selecting the antidiabetic medicinal product, a potential for hypoglycaemia with antidiabetic medication administration on non-Truqap dosing days should be taken in account.

Table 3: Recommended dose modification of Truqap for Hyperglycaemia

CTCAE Grade[a] and Fasting Glucose (FG)[b] values prior to Truqap dose	Recommendations[c]
Grade 1 > ULN160 mg/dL or > ULN8.9 mmol/L or HbA1C > 7%	No Truqap dose adjustment required. Consider initiation or intensification of oral anti-diabetic treatment.
Grade 2 > 160-250 mg/dL or > 8.9-13.9 mmol/L	Initiate or intensify oral anti-diabetic treatment without dose adjustment of Truqap. If FG does not decrease to ≤ 160 mg/dl (or ≤ 8.9 mmol/L) with treatment, interrupt Truqap for up to 28 days until FG level decrease to ≤ 160 mg/dL (or ≤ 8.9 mmol/L). If improvement to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) is reached within 28 days, restart Truqap at the same dose level and maintain initiated or intensified anti-diabetic treatment. If improvement to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) is reached after 28 days restart at one lower dose level and maintain initiated or intensified anti-diabetic treatment.

CTCAE Grade[a] and Fasting Glucose (FG)[b] values prior to Truqap dose	Recommendations[c]
Grade 3 > 250-500 mg/dL or > 13.9-27.8 mmol/L	Withhold Truqap and consult diabetologist/endocrinologist. Initiate or intensify oral anti-diabetic treatment. Consider additional anti-diabetic medicinal products such as insulin, as clinically indicated. Consider intravenous hydration and provide appropriate clinical management as per local guidelines. If FG decreases to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) within 28 days restart Truqap at one lower dose level and maintain initiated or intensified anti-diabetic treatment. If FG does not decrease to ≤ 160 mg/dL (or ≤ 8.9 mmol/L) within 28 days following appropriate treatment permanently discontinue Truqap.
Grade 4 > 500 mg/dL or > 27.8 mmol/L	Withhold Truqap and consult with diabetologist/endocrinologist Initiate or intensify appropriate anti-diabetic treatment. Consider insulin, (dosing and duration as clinically indicated), intravenous hydration and provide appropriate clinical management as per local guidelines. If FG decreases to ≤ 500 mg/dl (or ≤ 27.8 mmol/l) within 24 hours, then follow the guidance in the table for the relevant grade. If FG is confirmed at > 500 mg/dl (or ≥ 27.8 mmol/l) after 24 hours, permanently discontinue Truqap treatment.

[a] Grading according to NCI CTCAE Version 4.03.

[b] Considerations should be also given to increases in HbA1C.

[c] See section “Special warnings and special precautions” for further recommendations on monitoring of glycaemia and other metabolic parameters.

Diarrhoea

Consider secondary prophylaxis in patients with recurrent diarrhoea.

Table 4: Recommended dose modification of Truqap for Diarrhoea

CTCAE Grade [a]	Recommendations
Grade 1	No Truqap dose adjustment required. Initiate appropriate anti-diarrhoeal therapy, maximise supportive care and monitor as clinically indicated.

CTCAE Grade [a]	Recommendations
Grade 2	Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. Interrupt Truqap dose for up to 28 days until recovery to ≤ Grade 1 and resume Truqap dosing at same dose or one lower dose level as clinically indicated. If Grade 2 diarrhoea is persistent or recurring, maintain appropriate medical therapy and restart Truqap at one lower dose level, as clinically indicated.
Grade 3	Interrupt Truqap. Initiate or intensify appropriate anti-diarrhoeal treatment and monitor as clinically indicated. If the symptoms improve to ≤ Grade 1 in 28 days resume Truqap at one lower dose level. If the symptoms do not improve to ≤ Grade 1 in 28 days permanently discontinue Truqap
Grade 4	Permanently discontinue Truqap.

[a] Grading according to NCI CTCAE Version 5.0.

*Rash and other Skin Drug Reaction*s

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

Table 5: Recommended dose modification of Truqap for rash and other skin drug reactions

CTCAE Grade[a]	Recommendations
Grade 1	No Truqap dose adjustment required. Initiate emollients and consider adding an oral non-sedating antihistamine treatment as clinically indicated to manage symptoms.

CTCAE Grade[a]	Recommendations
Grade 2	Initiate or intensify topical steroid treatment and consider non-sedating oral antihistamines. If no improvement with treatment, interrupt Truqap. Resume at the same dose level once the rash becomes clinically tolerable.
Grade 3	Interrupt Truqap. Initiate appropriate dermatological treatment with topical steroid of moderate/ higher strength, non-sedating oral antihistamines and /or systemic steroids. If symptoms improve within 28 days to ≤ Grade 1, restart Truqap on one lower dose level. If the symptoms do not improve to ≤ Grade 1 in 28 days discontinue Truqap. In patients with reoccurrence of intolerable ≥ Grade 3 rash, consider permanent discontinuation of Truqap.
Grade 4	Permanently discontinue Truqap

[a] Grading according to NCI CTCAE Version 5.0.

Other toxicities

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

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

CTCAE Grade[a]	Recommendation
	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 or moderate CYP3A inhibitors

Co administration with strong CYP3A 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) (see section "Interactions") and patients should be monitored for the occurrence of toxicities due to potentially increased exposure to capivasertib.
When co administered with a moderate CYP3A inhibitor, reduce the dosage of Truqap to 320 mg twice daily.

Co administration with strong or moderate CYP3A inducers

Co administration with strong or moderate CYP3A inducers should be avoided.

Special populations

Elderly patients

No dose adjustment is required for elderly patients (see section ”Pharmacokinetics”). There are limited data in patients aged ≥ 75 years.

Patients with renal disorders

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 ”Pharmacokinetics”).

Patients with hepatic disorders

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 ”Pharmacokinetics”).

Children and adolescents

Truqap is not indicated for use in paediatric patients, as safety and efficacy of Truqap in children and adolescents have not been established.

Duration of treatment

Treatment with Truqap should continue until disease progression or unacceptable toxicity occurs.

Mode of administration

Truqap tablets should be swallowed whole with water and not chewed, crushed, dissolved, or divided. Truqap should not be ingested if it is broken, cracked, or otherwise not intact.

Contraindications

Prior severe hypersensitivity to the active substance or to any of the excipients listed in section ”Composition-Excipients”.
Please refer to fulvestrant SmPC for contraindications related to fulvestrant.

Warnings and precautions

Hyperglycaemia

Severe hyperglycaemia has been reported in patients treated with Truqap. In CAPItello-291, one event of ketoacidosis has been reported. Before initiating treatment with Truqap, inform patients about Truqap’s potential to cause hyperglycaemia and to immediately contact their healthcare professional if hyperglycaemia symptoms (e.g., excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss) occur. Patients should be tested for fasting blood glucose (FG) levels and HbA1C prior to treatment with capivasertib and at regular intervals during treatment. FG testing should be performed prior to the regular dose of Truqap. It is recommended to test FG at least every two weeks during the first month of treatment and at least once a month starting from the second month, and HbA1C every three months. 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 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. Monitoring of HbA1C, ketones (preferably in blood) and other metabolic parameters (as indicated), in addition to FG, is recommended in these patients.,In CAPItello-291,, the median time to first occurrence of hyperglycaemia was 15.0 days (range 1.0 -367 days). Based on the severity of hyperglycaemia, Truqap dosing may be interrupted, reduced, or permanently discontinued (see section ”Dosage/Administration”, Table 3).

The safety of Truqap in patients with Type 1 or Type 2 diabetes requiring insulin has not been studied as these patients were excluded from the study. Patients with history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

Diarrhoea

Diarrhoea has been frequently reported in patients treated with Truqap (see section 4.8).
In CAPItello-291 the median time to first occurrence of diarrhoea was 8.0 days (range 1-519 days). Based on the severity of diarrhoea, Truqap dosing may be interrupted, reduced, or permanently discontinued (see section ”Dosage/Administration”, Table 4). Advise patients to start anti diarrheal treatment at the first sign of diarrhoea, increase oral fluids if diarrhoea symptoms occur while taking Truqap. Maintenance of normovolemia and electrolyte balance is required in patients with diarrhoea to avoid complications related to hypovolemia and low electrolyte levels. There is an increased risk of diarrhoea after co-administration of capivasertib and metformin.

Rash and other skin drug reactions

Skin drug reactions, including erythema multiforme and dermatitis exfoliative generalised were reported in patients receiving Truqap (see section ”Undesirable effects”). Patients should be monitored for signs and symptoms of rash or dermatitis and based on severity of skin drug reactions the dosing may be interrupted, reduced, or permanently discontinued (see section ”Dosage/Administration”, Table 5). Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

Excipients of particular interest

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet i.e. it is almost "sodium-free".

Interactions

Effect of other medicinal products on Truqap

In vitro studies have demonstrated that capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes.

Co administration of a single dose of Truqap 400 mg after repeated dosing of acid-reducing agent rabeprazole 20 mg twice daily for 3 days in healthy subjects did not result in clinically relevant changes of the capivasertib exposure. In addition, a population pharmacokinetic analysis showed no significant impact of co administration of acid reducing agents on the pharmacokinetics of capivasertib in patients. Truqap can be taken with acid reducing agents.

Table 7: Drug interactions with Truqap that affect capivasertib

Strong CYP3A4 inhibitors[a]	
Data	In a study in healthy subjects, co-administration of multiple 200 mg doses of the strong CYP3A4 inhibitor itraconazole with a single 80 mg capivasertib dose increased capivasertib AUC and C_{max} by 95% and 70%, respectively, relative to a single 80 mg capivasertib dose given alone. At the therapeutic dose regimen, the predicted increase in capivasertib AUC and C_{max} by itraconazole is between 52% and 56%, and between 30% and 35%, respectively, over a dosing cycle.
Clinical impact	Concomitant use with a strong CYP3A4 inhibitor increases capivasertib concentration, which may increase the risk of Truqap toxicities.
Prevention or management	Concomitant use with a strong CYP3A inhibitor should be avoided. If it cannot be avoided, the dose of Truqap should be reduced.(see section ”Dosage/Administration”).
Examples[b]	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. Intake of high doses of grapefruit or grapefruit juice should be avoided.
Moderate CYP3A4 inhibitors[b]	
Data	Based on in vitro data and physiologically based pharmacokinetic models, the predicted increase in capivasertib AUC by verapamil and erythromycin is approximately 40% and by ritonavir (1.5 mg BD) less than 20%.
Clinical impact	Concomitant use with a moderate CYP3A4 inhibitor may increase capivasertib concentration, which may increase the risk of Truqap toxicities.
Prevention or management	The dose of Truqap should be reduced (see section ”Dosage/Administration”).

Examples [b]	Aprepitant, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole fluvoxamine, tofisopam, verapamil
Strong[c] or moderate[d] CYP3A4 inducers	
Data	Based on in vitro data and modelling, rifampicin is predicted to decrease capivasertib AUC by approximately 70%.
Clinical impact	Concomitant use with a strong or moderate CYP3A4 inducer decreases capivasertib concentration which may reduce the efficacy of Truqap (see section ”Pharmacokinetics”).
Prevention or management	Concomitant use of strong or moderate CYP3A4 inducers should be avoided.
Examples of strong CYP3A inducers[c]	Carbamazepine, phenytoin, rifampicin, St. John’s wort.
Examples of moderate CYP3A inducers[d]	Bosentan, cenobamate, dabrafenib, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, metamizole, mitapivat, nafcillin, pexidartinib, phenobarbital, rifabutin, semagacestat, sotorasib, talviraline, telotristat ethyl, thioridazine.

[a] Strong inhibitors increase the AUC of sensitive substrates for CYP3A4 (e.g. midazolam) ≥ 5-fold.

[b] Moderate inhibitors increase the AUC of sensitive substrates for CYP3A4 (e.g. midazolam) ≥ 2-fold and <5-fold.

[c] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[d] Strong inducers decrease the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) by ≥ 80%.

[e] Moderate inducers decrease the AUC of sensitive substrates for CYP3A4 (e.g., midazolam) by ≥ 50% to < 80%.

Co administration with the UGT2B7 inhibitor probenecid is predicted to cause an increase in capivasertib AUC of 23 to 37% over a dosing cycle. Simultaneous administration of strong/moderate CYP3A inhibitors and UGT2B7 inhibitors should be avoided.

Effect of Truqap on other medicinal products

Capivasertib inhibited CYP2C9, CYP2D6, CYP3A4 and UGT1A1, intestinal UGT1A4 metabolizing enzymes and BCRP, OATP1B1, 1B3, OAT3, OCT2, MATE1 and MATE2K drug transporters in *in vitro* studies.

Capivasertib induced CYP1A2, CYP2B6 and CYP3A4 in *in vitro* studies.

Table 8**: Drug interactions with Truqap that may affect other drugs**

Substrates of CYP3A	
Data	Co administration of Truqap at the recommended dose with midazolam (a sensitive CYP3A substrate), increased the AUC of midazolam by 15% on the 3rd off-dosing day and by 77% on the 4th on-dosing day of capivasertib which shows that capivasertib is a weak CYP3A inhibitor
Clinical impact	Concentration of drugs that are primarily eliminated via CYP3A metabolism may be increased by concomitant use with Truqap. This may result in increased toxicity of these drugs, depending on their therapeutic window.
Prevention or management	Dose adjustment may be required for drugs that are primarily eliminated via CYP3A metabolism and have a narrow therapeutic window. Refer to specific guidance in the prescribing information for these drugs. Concomitant use should be avoided if possible.
Examples[a]	Carbamazepine, cyclosporine, fentanyl, pimozide, simvastatin, tacrolimus.
Interactions with hepatic transporters (OATP1B1, OATP1B3)	
Clinical impact	The concentration of drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3 may increase by concomitant use with Truqap (see section ”Pharmacokinetics”). This may result in increased toxicity.
Prevention or management	Depending on their therapeutic window, dose adjustment may be required for drugs that are sensitive to inhibition of OATP1B1 and/or OATP1B3. Refer to specific guidance in the prescribing information for these drugs. Concomitant use should be avoided if possible.
Examples[a]	Simvastatin,.Atorvastatin Rosuvastatin
Interactions with renal transporters (MATE1, MATE2K, OCT2)	
Clinical impact	The concentration of drugs that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by concomitant use with Truqap (see section ”Pharmacokinetics”). This may result in increased toxicity.

	Transient serum creatinine increases may be observed during treatment with Truqap due to inhibition of OCT2, MATE1 and MATE2K by capivasertib.
Prevention or management	Depending on their therapeutic window, dose adjustment may be needed for drugs that are sensitive to inhibition of MATE1, MATE2K, OCT2. Refer to specific guidance in the prescribing information for these drugs.
Examples[a]	Dofetilide, procainamide, Metformin.

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

Pregnancy, lactation

Contraception

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Truqap. A pregnancy test should be performed on women of childbearing potential prior to initiating treatment, and verified as negative prior to initiating treatment, and re-testing considered throughout treatment.
Patients should be advised to use effective contraception during treatment with Truqap and for the following periods after completion of treatment with Truqap: at least 4 weeks.

Pregnancy

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

Lactation

It is not known whether capivasertib or its metabolites are excreted in human milk. Exposure to capivasertib was confirmed in suckling rat pups which may indicate the excretion of capivasertib in milk. A risk to the suckling child cannot be excluded (see section ”Preclinical data”). 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 ”Preclinical data”).
Please refer to section ”Pregnancy, lactation” of the prescribing information for fulvestrant.

Effects on ability to drive and use machines

Truqap has no influence on the ability to drive and use machines. However, during treatment with capivasertib, fatigue has been reported and those patients who experience this symptom should be advised to observe caution when driving or operating machinery.

Undesirable effects

Summary of the safety profile

The safety profile of Truqap is based on pooled data (n=526) from studies with combination of Truqap with fulvestrant or abiraterone in breast or prostate cancer.
The most common undesirable effects (reported at a frequency of ≥ 20%), were diarrhoea (71.9%), rash (41.3%), nausea (39%), fatigue (26%) and vomiting (23.4%). The most common grade 3 or 4 adverse reactions (reported at frequency ≥ 2%) were rash (13.1%), diarrhoea (9.1%) and hyperglycaemia (3.2%).
Serious undesirable effects reported in ≥ 1% of patients receiving Truqap plus fulvestrant included rash (2.3%), diarrhoea (2.1%), and vomiting (1.5%). Regardless of the causal relationship, 7 deaths (1.3%) were reported with TRUQAP plus fulvestrant for reasons other than their underlying malignancy. Causes of death included aspiration pneumonia, sepsis, atypical chest infection, acute kidney injury, acute myocardial infarction, haemorrhage, and cerebral haemorrhage.
In the same pool (except for 1 study in combination with fulvestrant with 69 patients) dose reductions due to undesirable effects were reported in 67 (14.7%) patients. The most common undesirable effects (reported at frequency ≥ 2%) leading to dose reduction of Truqap were diarrhoea (6.6%) and rash (3.9%).
Treatment discontinuation due to undesirable effects occurred in 42 (9.2%) patients. The most common undesirable effects (reported at frequency ≥ 2%) leading to treatment discontinuation were rash (3.7%).

List of adverse reactions

The following Adverse Drug Reactions have been reported for Truqap in combination with fulvestrant or abiraterone and 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 9: Undesirable effects

MedDRA SOC	MedDRA Term	Any Grade (%)	Grade 3 or 4 (%)
Infections and infestations	Urinary Tract Infection[1]	Very Common 12.2	1.7
Blood and lymphatic system disorders	Anaemia	Very Common 11.0	1.5
Immune system disorders	Hypersensitivity[2]	Common 1.3	0.2
Metabolism and nutrition disorders	Hyperglycaemia[3]	Very Common 21.1	3.2
	Decreased appetite	Very Common 17.1	0.4
	Diabetic metabolic decompensation	Uncommon 0.4	0.2
	Diabetic ketoacidosis	Uncommon 0.2	0.2
Nervous system disorders	Dysgeusia	Common 5.7	0
Gastrointestinal disorders	Diarrhoea[4]	Very Common 71.9	9.1
	Nausea	Very Common 39	1.1
	Vomiting	Very Common 23.4	1.9
	Stomatitis[5]	Very Common 15.8	1.3
	Dyspepsia	Common 4.9	0
Renal and Urinary Disorders	Acute Kidney Injury	Common 2.9	1.5
Skin and subcutaneous tissue disorders	Rash[6]	Very Common 41.3	13.1
	Pruritis	Very Common 11.6	0.4
	Dry skin	Common 7.0	0
	Erythema multiforme	Common 1.1	0.6

Table 9: Undesirable effects

MedDRA SOC	MedDRA Term	Any Grade (%)	Grade 3 or 4 (%)
	Drug Eruption	Uncommon 0.8	0.8
	Dermatitis	Uncommon 0.6	0
	Dermatitis exfoliative generalised	Uncommon 0.4	0.4
	Toxic Skin Eruption	Uncommon 0.2	0
General disorders and administration site conditions	Fatigue	Very Common 26	1.0
	Mucosal inflammation	Common 2.1	0.2
Investigations	Blood creatinine increased	Common 4.9	0.2
	Glycosylated haemoglobin increased	Common 1.5	0

MedDRA term gives the undesirable effect grouped term.
[1] Urinary Tract Infection includes urinary tract infection and cystitis.
[2] Hypersensitivity includes hypersensitivity and drug hypersensitivity.
[3] Hyperglycaemia includes hyperglycaemia and blood glucose increased.
[4] Diarrhoea includes diarrhoea
[5] Stomatitis includes stomatitis, aphthous ulcer and mouth ulceration.
[6] Rash includes erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic.

Description of specific undesirable effects

Description of specific undesirable effects is based on CAPItello-291 study in combination with fulvestrant in patients with locally advanced (inoperable) or metastatic HR positive and HER2 negative breast cancer (Please see Section Clinical Efficacy for details).

Hyperglycaemia

Hyperglycaemia of any grade occurred in 60 (16.9%) patients and grade 3 or 4 occurred in 8 (2.3%) patients receiving Truqap. In the study, dose reduction was required in 2 (0.6%) patients and 1 (0.3%) patient discontinued treatment due to hyperglycaemia. In the 60 patients with hyperglycaemia, 28 (46.7%) patients were treated using anti-hyperglycaemic medication (including insulin in 10 (16.7%) patients).

Diarrhoea

Diarrhoea occurred in 257 (72.4%) patients receiving Truqap. Grade 3 and/or 4 diarrhoea occurred in 33 (9.3%) patients. Dose reduction was required in 28 (7.9%) patients and 7 (2.0%) patients discontinued Truqap due to diarrhoea. In the 257 patients with diarrhoea, anti-diarrheal medication was required in 59% (151/257) of patients to manage diarrhoea symptoms.

Cutaneous reactions

Rash (including erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic) was reported in 143 (40.3%) patients. Grade 3 and/or 4 occurred in 44 (12.4%) of patients who received capivasertib. Dose reduction was required in 16 (4.5%) patients and 16 (4.5%) patients discontinued Truqap due to rash.

Overall cutaneous reactions CTCAE ≥Grade 3 ~~skin adverse reactions~~ (including erythema multiforme, rash, rash maculo-papular, rash papular, rash erythematous, rash macular, rash pruritic, erythema, drug eruption, dermatitis exfoliative generalised) were reported in 53 patients (14.9%). 27 out of the 53 patients who experienced ≥ Grade 3 skin ADRs, required systemic corticosteroids and 29 patients were treated with topical corticosteroids.

Elderly patients

In CAPItello-291, analyses of the safety of Truqap comparing patients ≥ 65 years of age to younger patients suggest a higher incidence of Grade 3-5 adverse events (50% versus 22%), dosage reductions (30% versus 13%), dose interruptions (49% versus 20%), and permanent discontinuations (19% versus 7%), respectively.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

ATC code

L01EX27

Mechanism of action

Capivasertib is a potent inhibitor of the kinase activity of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3). AKT is involved in the regulation of 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 inhibits the phosphorylation of downstream AKT substrates such as glycogen synthase kinase 3-β (GSK3β) and proline-rich AKT substrate of 40 kilodaltons (PRAS40) and reduces growth of a range of cell lines derived from solid tumours, including multiple breast cancer cell lines, and haematological disease.
Combined treatment with capivasertib and fulvestrant demonstrated a greater anti-tumour response in a range of human breast cancer Patient derived xenografts (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 (90% CI: 2.77-4.97) at the mean steady state C_{max} following 400 mg twice daily.

Clinical efficacy

CAPItello-291 was a randomized, double-blind, placebo-controlled study 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 following recurrence or progression on or after aromatase inhibitor (AI) based treatment. Patients in the *PIK3CA/AKT1/PTEN* altered population have a tumour carrying at least

one molecular alteration in *PIK3CA, AKT1* or *PTEN* genes as detected using a validated in vitro diagnostic test.

Patient tissue alteration status should be determined using a validated test to identify one or more genomic alterations in *AKT1* (any short variant with protein effect E17K), *PIK3CA* (R88Q, N345K, C420R, E542K, E545A/D/G/K/Q, Q546E/K/P/R, M1043V/I, H1047L/R/Y and G1049R short variants), or *PTEN* (C124R/S, G129E/V/R, R130Q/G/L/P, C136R/Y, S170R and R173C short variants, or any *PTEN* loss of function alteration (including nonsense, frameshift, splice site alteration, any homozygous deletion of one or more exons, any rearrangement).

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, including QTcF > 470 msec, any factors that increased the risk of QTc prolongation or risk of arrhythmic events or risk of cardiac function impairment, and symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy.

A total of 708 patients were randomized 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. Randomization 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 randomization to determine *PIK3CA/AKT1/PTEN* alteration status retrospectively by central testing.

Demographic and baseline characteristics were well balanced between arms. Of the 289 patients whose tumors were *PIK3CA/AKT1/PTEN*-altered, the median age was 59 years (range 34 to 90); female (99%); White (52%), Asian (29%), Black (1.0%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (65.7%), 1 (33.9%), ~~21.8~~18 % were pre/peri menopausal. 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 71~~0.1~~% of patients. Chemotherapy for locally advanced (inoperable) or metastatic disease was reported in 18.~~2~~% of patients. Patient demographics for those whose tumours have *PIK3CA* alterations (76% of patients), *AKT1* alterations (13% of patients) and *PTEN* alterations (17% of patients) 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 Tumors (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 patient whose tumours have *PIK3CA/AKT1/PTEN* alterations. PFS results by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. A preliminary assessment of OS in the overall population (28% maturity) and altered population (30% maturity) at the time of the primary PFS analysis does not suggest a detrimental effect on survival of treatment with capivasertib plus fulvestrant compared with placebo plus fulvestrant.

Efficacy results for and patient whose tumours have *PIK3CA/AKT1/PTEN* alterations are presented in table 10.

Table 10: Progression-free Survival, by Investigator Assessment in patient whose tumours have *PIK3CA/AKT1/PTEN* alterations.

	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.

PFS results for patients treated with Truqap plus fulvestrant were consistent with the results of the primary analysis in all pre-specified subgroups, including prior exposure to CDK4/6 inhibitors, as well as in the non-changed tumor population, which included patients with confirmed unchanged tumor and patients with no available test result.

Pharmacokinetics

Capivasertib pharmacokinetics have been characterized in healthy subjects and patients with solid tumours. The systemic exposure (AUC and C_{max}) increased approximately proportionally to the dose over the 80 to 640 mg dose range when given to patients. Following intermittent dosing of capivasertib 400 mg twice daily, 4 days on, 3 days off, steady-state levels are predicted to be attained on every 3rd and 4th dosing day each week, starting from week 2. During the off dosing days, the plasma concentrations are low (approximately 0.5% to 15% of the steady state C_{max}).

Absorption

Capivasertib is rapidly absorbed with peak concentration (C_{max}) observed at approximately 1-2 hours in patients. The mean absolute bioavailability is 29%.

Food Effect

When capivasertib was administered after a high-fat, high-calorie meal (approximately 1000 kcal), the fed to fasted ratio was 1.32 and 1.23, for AUC and C_{max}, respectively, compared to when given after an overnight fast. When capivasertib was administered after a low-fat, low-calorie (approximately 400 kcal), the exposure was similar to that after fasted administration with fed to fasted ratios of 1.14 and 1.21, for AUC and C_{max}, respectively. Co-administration with food did not result in clinically relevant changes to the exposure.

Distribution

The mean volume of distribution (Vss) was 205 L after intravenous administration to healthy subjects. Capivasertib is not extensively bound to plasma protein (percentage unbound 22%) and the blood/plasmaratio is 1.40.

Metabolism

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 in plasma. Capivasertib accounted for 9.2% of total circulating drug-related material in plasma. No active metabolites have been identified.

Elimination

The effective half-life after multiple dosing in patients was 8.3 hours. The mean total plasma clearance was 38 L/h after a single intravenous administration to healthy subjects. The mean total

oral plasma clearance was 60 L/h after single oral administration and decreased by 8% after repeated dosing of 400 mg twice daily.
Following single oral dose of 400 mg, the mean total recovery of radioactive dose was 45% from urine and 50% from faeces. Renal clearance was 21% of total clearance after intravenous administration. Capivasertib is primarily eliminated by metabolism.

Kinetics in specific patient groups

Effect of race, age, gender and weight

There were no clinically significant differences in pharmacokinetics of capivasertib based on race/ethnicity (including White and Asian patients), gender or age. There was a statistically significant correlation of apparent oral clearance of capivasertib to body weight. Compared to a patient with a body weight of 66 kg, a 47 kg patient is predicted to have 12% higher AUC. There is no basis for dose modification based on body weight as the predicted effect on capivasertib exposure was small.

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. No dose adjustment is required for patients with mild hepatic impairment.
Based on limited data the AUC and C_{max} was 17% and 13% higher respectively in patients with moderate hepatic impairment (bilirubin > 1.5 ULN to ≤ 3 ULN), compared to patients with normal hepatic function. There is limited data in patients with moderate hepatic impairment (n=7) and no data in severe hepatic impairment.

Renal impairment

Based on population pharmacokinetic analyses, AUC and C_{max} were 1% higher in patients with mild renal impairment (creatinine clearance 51 to 80 mL/min), compared to patients with normal renal function. AUC and C_{max} were 16% higher in patients with moderate renal impairment (creatinine clearance 31 to 50 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).

Preclinical data

Repeat-dose toxicity

The major target organs or systems for toxicity were insulin signalling (increased levels of glucose and insulin in mice, rats and dogs), the male reproductive organs (tubular degeneration in mice, rats and dogs), and the renal system in rats and dogs (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. except for the changes in the testes and epididymides which were present at 28 days off dose but at a reduced severity in rats. 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 were also seen in dogs (QTc interval prolongation, increased cardiac contractility, and decreased blood pressure), which occurred at plasma concentrations higher than those in humans (approximately 1.5 to 3 times) at the recommended dose of 400 mg twice daily (based on total 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

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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging.
Keep out of the reach of children.

Instructions for handling

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

Authorisation number

69300

Packs

Truqap 160 mg Film-coated tablets: Packs with 64 Film-coated tablets [A].
Truqap 200 mg Film-coated tablets: Packs with 64 Film-coated tablets [A].

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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