Taiwan Food and Drug Administration

Assessment Report

Trade Name：泛抑癌®膜衣錠 160 毫克、200 毫克/
TRUQAP® Film-Coated Tablets 160 mg、 200 mg

Active Ingredient：capivasertib

License Number：MOHW-PI 028821、MOHW-PI 028820

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date： 113/11/06

Indication:
Truqap 與 fulvestrant 併用可治療患有荷爾蒙受體(HR)陽性、第二型人類表皮生長因子受體(HER2)陰性及具 PIK3CA/AKT1/PTEN 任一變異，且曾經接受內分泌治療，但疾病復發或惡化之局部晚期或轉移性乳癌成人病人。

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

Background Information

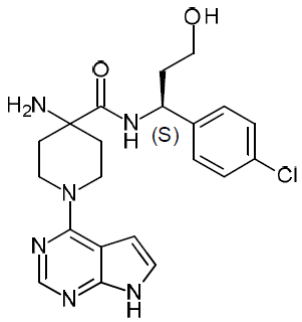
Trade Name	泛抑癌® 膜衣錠 160 毫克、200 毫克 TRUQAP® Film-Coated Tablets 160 mg、200 mg
Active Ingredient(s)	capivasertib
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	Film-Coated Tablets 160 mg、200 mg
Indication	Truqap 與 fulvestrant 併用可治療患有荷爾蒙受體(HR)陽性、第二型人類表皮生長因子受體(HER2)陰性及具 PIK3CA/AKT1/PTEN 任一變異，且曾經接受內分泌治療，但疾病復發或惡化之局部晚期或轉移性乳癌成人病人。
Posology	400 mg orally twice daily for 4 days followed by 3 days off
Pharmacological Category ATC Code	L01EX27

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, is chemically designated as 4-amino-*N*-[(1*S*)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-4-piperidinecarboxamide and has the following structure:



It is a white to off-white crystalline powder. The molecular formula and the molecular weight are $C_{21}H_{25}ClN_6O_2$ and 428.92 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of capivasertib has been confirmed by elemental analysis, infrared spectrophotometry (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV spectrophotometry. Stereochemistry is determined by single crystal X-ray diffraction analysis.

Adequate specification has been presented for the drug substance and the test items include description, identification, assay, organic impurities, chiral impurity, residual solvents, water content and particle size distribution. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is a film-coated tablet for oral administration containing 160 mg or 200 mg capivasertib. Capivasertib 160 mg tablets are presented as beige, round, biconvex, film-coated tablets, approximately 10 mm in diameter. The 160 mg tablets are marked with “CAV” above “160” on one side and plain on the reverse. Capivasertib 200 mg tablets are presented as beige, capsule-shaped, biconvex, film-coated tablets, approximately 14.5 x 7.25 mm. The 200 mg tablets are marked with “CAV200” on one side and plain on the reverse. The specifications for the excipients used in the film-coated tablets formulation are adequate.

Adequate specification has been presented for the drug product and the test items include description, identification, assay, degradation products, dissolution and uniformity of dosage units. Analytical methods are described and well validated. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications.

Stability studies of the drug product under long term conditions (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 24 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf-life of the drug product can be granted for 24 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Capivasertib is a selective inhibitor of all 3 isoforms of the serine/threonine kinase AKT (AKT1, AKT2, and AKT3). In vitro, capivasertib inhibited all 3 AKT isoforms, as well as p70S6K and PKA, with IC50 values in the low-nanomolar range. Capivasertib also inhibited other kinases, primarily AGC kinases, with less potency than AKT, and inhibited ROCK1 and ROCK2 with IC50 values in the mid- to high-nanomolar range. In cancer cell lines, capivasertib suppressed phosphorylation of the AKT substrates GSK3β, PRAS40, and the distal biomarker S6, with IC50 values from 70 nM to 2.57 μM. Capivasertib showed minimal inhibition activity against cellular ROCK. The major human metabolite, AZ14102143, did not affect AKT substrate phosphorylation. In vitro, capivasertib monotherapy reduced cell proliferation in cell lines with or without PIK3CA/AKT1/PTEN gene alterations. Combined with fulvestrant it showed anti-proliferative effect in two ER+ and two palbociclib-resistant breast cancer cell lines.

In vivo, oral capivasertib treatment in mice with various xenografts or PDX explants, including ER+ breast cancer models with PIK3CA/AKT1/PTEN alterations, led to dose-dependent tumor growth inhibition. PK/PD analysis revealed a dose-dependent reduction in phosphorylation of PRAS40, GSK3β, and S6 in the xenografts. In ER+ breast cancer xenograft models, both palbociclib-sensitive and -resistant, with or without PI3KCA/AKT1/PTEN alterations, combining capivasertib with fulvestrant generally enhanced anti-tumor effects compared to either treatment alone. Decreased phosphorylation of AKT and mTOR downstream targets, along with key cell cycle components, was observed in some models.

Secondary pharmacology studies showed that capivasertib was active against 8 out of 333 receptors, ion channels, transporters, and enzymes, with IC50 values from 0.47 to 62.3 μM. Only ROCK1, with an IC50 less than the clinical unbound Cmax (0.717 μM), was considered potentially relevant. Capivasertib showed no significant activity in 7 cardiac ion channels, with no IC50 at concentrations up to 139 times the clinical unbound Cmax.

In a safety pharmacology study in rats, capivasertib reduced motor activities and touch response, and inhibited gastric emptying in a dose-dependent manner, with no respiratory effects. The unbound Cmax at NOEL for the CNS, GI, and respiratory functions was 0.9- and 5-fold of the clinical unbound Cmax. In dogs, capivasertib caused decreased heart rate for up to 8 hours, peak blood pressure drop with recovery in 4 hours, prolonged QTcR, increased LVdP/dt+, and elevated glucose and insulin after

a single oral dose. The unbound plasma concentration at NOAEL (1 hour post-dose) was 0.4 times the clinical unbound Cmax. In vitro, capivasertib inhibited the hERG channel with an IC50 of 102-fold clinical unbound Cmax. In rats, doses ≥ 100 mg/kg led to glucosuria with diuresis, and increased excretion of sodium, chloride, potassium, and phosphate, with altered plasma phosphorous and potassium levels. A NOEL was not determined.

2.2.2 Toxicological Studies

GLP repeated-dose toxicity studies of capivasertib were conducted in mice (1 month), rats (up to 6 months), and dogs (up to 9 months). Major toxicity targets included insulin signaling, cardiovascular system, male reproductive organs, liver, kidneys, hypothalamic-pituitary axis, and hematopoietic system. Capivasertib's pharmacology largely caused observed toxicities, such as elevated glucose and insulin, along with effects like glycosylated hemoglobin, liver glycogen accumulation, polyuria, glucosuria, proteinuria, and increased water consumption, sometimes with kidney changes. In a 1-month dog study, QTc prolongation and increased cardiac contractility occurred at doses approximately 0.7- and 1.9-fold of the clinical dose exposure. Most toxicities in 1-month rat and dog studies were reversible after a 1-month recovery, except for changes in male reproductive organs. Capivasertib exposures at NOAELs in 6-month rat and 9-month dog studies provided safety margins of < 1-fold relative to the clinical dose AUC.

Capivasertib tested negative in the Ames assay, mouse lymphoma gene mutation assay, and Comet assay, but was positive in one of two rat micronucleus assays at 150 mg/kg. Per ICH S9, a carcinogenicity study is not needed for the proposed indication.

A 6-month rat toxicity study showed capivasertib had no impact on mating performance and fertility at any tested doses, though organ weight decrease and pathological changes in male reproductive organs were seen at the highest dose. The male fertility was 1.4 times the human exposure at the recommended clinical dose (AUC-based). No dedicated female fertility study was done, but the 1-month rat study showed reversible decreases in female reproductive organ weights without microscopic findings. In a GLP preliminary EFD and early postnatal study, maternal toxicity, such as reduced body weight gain, food consumption, and increased blood glucose occurred at doses up to 150 mg/kg/day, which is about 0.8 times the human exposure at the clinical dose (AUC-based). Administering 150 mg/kg/day from gestation days 2 to 16 led to embryofetal toxicity, including increased minor fetal visceral variations, post-implantation loss, and reduced uterine and fetal weights. Administering 150 mg/kg/day from gestation Day 6

to lactation Day 6 reduced pup and litter weights, and capivasertib was present in suckling pups, indicating possible milk excretion.

Lastly, capivasertib was not phototoxic in vitro.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Capivasertib pharmacokinetic parameters are presented as the mean [%coefficient of variation (%CV)], unless otherwise specified. The capivasertib steady-state AUC is 8,069 h·ng/mL (37%) and C_{max} is 1,371 ng/mL (30%). Steady-state concentrations are predicted to be attained on the 3rd and 4th dosing day of each week, starting week 2. Capivasertib plasma concentrations are approximately 0.5% to 15% of the steady state Cmax during the off-dosing days. Capivasertib AUC and C_{max} are proportional with dose over a range of 80 to 800 mg (0.2 to 2 times the approved recommended dosage). Following a single oral dose of 400 mg capivasertib tablet, the absorption was rapid with the median t_{max} for capivasertib was 1-2 hours post-dose. The geometric mean absolute bioavailability of capivasertib following a 400 mg capivasertib oral dose was 29%. No clinically meaningful differences in capivasertib pharmacokinetics were observed following administration of Capivasertib with a high-fat meal or a low-fat meal. The steady state oral volume of distribution is 1,847 L (36%). Capivasertib plasma protein binding is 22% and the plasma-to-blood ratio is 0.71.

Results from in vitro studies suggest that capivasertib is primarily metabolized by CYP3A4 and UGT2B7. The major metabolite in human plasma was identified as an ether glucuronide (AZ14102143) that accounted for 83% of total drug-related material and was inactive against AKT. A minor oxidative metabolite was detected and quantified at much lower levels (2%), while capivasertib accounted for 15% of total circulating drug-related material. No active metabolites have been identified. Following a single radiolabeled oral dose of 400 mg, the mean total recovery was 45% from urine and 50% from feces. The half-life is 8.3 hours and the steady-state oral clearance is 50 L/h (37% CV). Renal clearance was 21% of total clearance.

2.3.2. Interaction Studies

In a study in healthy subjects, co-administration of the strong CYP3A4 inhibitor itraconazole with a single 80 mg capivasertib dose increased capivasertib total exposure (AUC_{inf}) and C_{max} by 95% (90% CI: 82%, 110%) and 70% (90% CI: 56%, 86%), respectively, relative to a single 80 mg dose of capivasertib given alone. Erythromycin and verapamil (moderate CYP3A inhibitors) are predicted to increase capivasertib AUC by up to 1.5-fold and C_{max} by up to 1.3-fold. Therefore, avoid concomitant use with strong CYP3A inhibitors, if concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the dosage of capivasertib to 320 mg orally twice daily for 4 days followed by 3 days off is recommended. When concomitantly used with a

moderate CYP3A inhibitor, reduce the dosage of capivasertib to 320 mg orally twice daily for 4 days followed by 3 days off is recommended.

Rifampicin (strong CYP3A4 inducer) is predicted to decrease capivasertib AUC by 70% and C_{max} by 60%. Efavirenz (moderate CYP3A4 inducer) is predicted to decrease capivasertib AUC by 60% and C_{max} by 50%. Thus, avoid concomitant use of capivasertib with strong or moderate CYP3A inducers is recommended.

Probenecid (UGT2B7 inhibitor) is not predicted to have a clinically meaningful effect on capivasertib pharmacokinetics. Rabeprazole (gastric acid reducing agent) did not have a clinically meaningful effect on capivasertib pharmacokinetics. No dose adjustment for capivasertib is required when co-administered with UGT2B7 inhibitors and acid reducing agents.

Concomitant use of capivasertib increased midazolam (CYP3A substrate) AUC by 1.8-fold on day 4 and by 1.2-fold on day 12 (fourth on day of the intermittent capivasertib dosing schedule). Dose adjustment may be required for drugs that are primarily eliminated via CYP3A metabolism and have a narrow therapeutic window. In addition, capivasertib is predicted to increase desipramine (CYP2D6 substrate) AUC by up to 2.1-fold on day 4. Concomitant use of capivasertib with warfarin (CYP2C9 substrate) is not predicted to have a clinically meaningful effect on warfarin pharmacokinetics. capivasertib is predicted to increase raltegravir (UGT1A1 substrate) AUC by up to 1.7-fold on day 4.

In Vitro studies were shown that capivasertib inhibits BCRP, OATP1B1, OATP1B3, OAT3, MATE1, MATE2-K, and OCT2. The exposure of medicinal products that are sensitive to inhibition of BCRP, OATP1B1 and/or OATP1B3, if they are metabolized by CYP3A4, may increase by co-administration with capivasertib. 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 metabolized by CYP3A4 (e.g. simvastatin). The exposure of medicinal products that are sensitive to inhibition of MATE1, MATE2K and/or OCT2 may increase by co-administration with capivasertib. 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). Transient serum creatinine increases may be observed during treatment with capivasertib due to inhibition of OCT2, MATE1 and MATE2K by capivasertib.

2.3.3. Special Populations

No clinically significant differences in capivasertib pharmacokinetics were observed based on age (26 to 87 years) according to population PK analysis. There are limited data in patients aged ≥ 75 years. The population PK analysis (females = 88%) indicated that sex did not have a significant effect on the PK of capivasertib. Therefore, no dose adjustment is required based on age and gender. The population PK analysis identified body weight as having an impact on the CL_{ss}/F, $AUC_{12h,ss}$ and $C_{max,ss}$ of capivasertib. There is no basis for dose modification based on body weight as changes in body weight were related to limited (within 20%) changes of CL.

Capivasertib can be administered to patients with mild and moderate renal impairment (creatinine clearance ≥ 30 mL/min) without any dose adjustments based on population PK analysis. Capivasertib is not recommended for patients with severe renal impairment, as safety and PK have not been studied in these patients. No dosage modification is recommended for patients with mild hepatic impairment (bilirubin ≤ upper limit of normal (ULN) and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST) based on population PK analysis. The effect of moderate (bilirubin > 1.5 to 3x ULN and any AST) hepatic impairment is not fully characterized with limited data (7 patients). Monitor patients with moderate (bilirubin > 1.5 to 3x ULN and any AST) hepatic impairment for adverse reactions is recommended, due to potential increased capivasertib exposure. Capivasertib is not recommended for patients with severe (bilirubin > 3x ULN and any AST) hepatic impairment, as safety and PK have not been studied in these patients.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study CAPItello-291 (D3615C00001) was reviewed to evaluate the efficacy of capivasertib (AZD5363) + fulvestrant in patients with locally advanced (inoperable) or metastatic HR+/HER2- breast cancer following recurrence or progression on or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor. The dual primary endpoints were investigator-assessed progression-free survival (PFS) by RECIST v1.1 assessed both in the Overall Population and in the PIK3CA/AKT1/ PTEN-altered subgroup (Altered Population).

At data cut-off of 15 August 2022 (DCO1), the study met both dual primary endpoints. Treatment with capivasertib + fulvestrant resulted in a statistically significant improvement in investigator-assessed PFS by RECIST 1.1 compared with placebo + fulvestrant in both the Overall Population (hazard ratio: 0.60; 96.5% CI: 0.50, 0.72; $p < 0.001$) and the Altered Population (hazard ratio: 0.50; 95% CI: 0.38, 0.65; $p < 0.001$).

2.4.2 Safety Results

As expected in a placebo-controlled study, the incidence of AEs was higher in the capivasertib + fulvestrant arm than in the placebo + fulvestrant arm, regardless of AE categories or populations in CAPItello-291. The most common AEs (reported at a frequency of ≥ 20%), were: diarrhea (72.4%), rash (40.3%), nausea (34.6%), fatigue (20.8%), vomiting (20.6%) in CAPItello-291. In CAPItello-291, the most common AEs of CTCAE Grade 3 or higher by preferred term (> 5% of patients) were diarrhea (9.3%), rash maculopapular (6.2%), and rash (5.4%) in the capivasertib + fulvestrant arm. The incidence of any SAEs during CAPItello-291 was 16.1% (57 patients) in the capivasertib + fulvestrant arm versus 8.0% (28 patients) in the placebo + fulvestrant arm. The most common SAEs (≥ 2 patients) were diarrhea, rash maculopapular, vomiting, acute kidney injury, hyperglycemia, asthenia, pneumonia aspiration, and sepsis in the capivasertib + fulvestrant arm.

The incidence of AEs leading to dose modifications of capivasertib/placebo was higher in the capivasertib + fulvestrant arm (43.9%) compared with the placebo + fulvestrant arm (12.3%). The AEs most commonly leading to dose modifications of capivasertib (> 3% of patients) were diarrhea, rash maculo-papular, rash, vomiting, and nausea. In conclusion, precaution should be taken for the adverse reactions of Hyperglycemia, Diarrhea and Rash maculo-papular.

2.5 Bridging Study Evaluation

Based on cross-study comparisons, the exposure in the Japanese population was slightly higher than in the Western population, and the differences in exposure between different ethnic groups were not considered to be clinically significant. According to population PK analysis, the results shown that the steady-state exposure (AUCss and Cmax) in the East Asian population and the Western population were similar.In addition, it's not metabolized by enzymes known to show genetic polymorphism and is not a prodrug. Thus, capivasertib showed none to minimally ethnically sensitive in PK's aspect.

Subgroup analysis of East Asians in CAPItello-291 were submitted to support BSE. A total of 177 (25%) participants were enrolled at sites of Japan, South Korea and Taiwan. Compared to Non-Asian subgroup, East Asian participants had less proportion of patients with prior CDK4/6 inhibitors and less prior lines of therapy, and higher proportion with altered PI3K/AKT/PTEN at Baseline. The median PFS for capivasertib + fulvestrant vs. placebo + fulvestrant was 10.9 vs 3.7 months in East Asian patients (HR [95%CI]: 0.49 [0.29, 0.83]). There were comparable responses with regards to efficacy and safety between the East Asian and Non-Asian subgroups in CAPItello-291. There is no strong evidence suggesting that there is any clinically relevant ethnic difference between the East Asian patients and patients from the Western countries. Further bridging study is not needed.

2.6 Conclusion

This multidisciplinary review recommends approval for TRUQAP® (capivasertib) indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-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.

3. Post-Marketing Requirements

1. Submit final report of FDA-required PMR 4548-3 and PMR 4548-4 after study completion.
2. Submit the final overall survival (OS) analysis and CSR of CAPItello-291 while available.