# DRUG NAME: Capivasertib

**SYNONYM(S):** AZD5363[1]

**COMMON TRADE NAME(S):** TRUQAP®

**CLASSIFICATION:** molecular targeted therapy

*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.*

## MECHANISM OF ACTION:

Capivasertib is an orally administered kinase inhibitor that targets all three isoforms of serine/threonine AKT (AKT1, AKT2 and AKT3). AKT is a key component of the phosphoinositide 3-kinase (PI3K) signaling pathway regulating cell proliferation, survival, and metabolism. AKT activation in tumour cells occurs through various mechanisms, including mutations in AKT1 or PIK3 catalytic subunit (PIK3CA), loss of phosphatase and tensin homolog (PTEN), or activation of upstream signaling pathways. By binding to AKT, capivasertib inhibits phosphorylation of downstream substrates, preventing cell proliferation and tumour growth. *In vitro*, capivasertib has demonstrated antitumor activity against various cancer cell lines with or without genetic alterations in PIK3CA, AKT1 or PTEN.[1-3]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Oral Absorption | $T_{max}$ = 1.4 h; bioavailability = 29%; food has no clinically meaningful effect on pharmacokinetics | |
| Distribution | widely distributed to tissues based on volume of distribution | |
| | cross blood brain barrier? | yes[4] |
| | volume of distribution | 322-1847 L at steady state[3,5] |
| | plasma protein binding | 78% |
| Metabolism | primarily metabolized by CYP3A4 and UGT2B7 enzymes | |
| | active metabolite(s) | no information found |
| | inactive metabolite(s) | M11 (AZ14102143)[6] |
| Excretion | renal clearance of 8.3 L/h suggests active renal tubular secretion[6] | |
| | urine | 45% |
| | feces | 50% |
| | terminal half life | 8.3 h |
| | clearance | 50 L/h |
| Sex | no clinically significant difference | |
| Elderly | no clinically significant difference | |
| Ethnicity | no clinically significant differences | |

Adapted from standard reference[1,3] unless specified otherwise.

## USES:

***Primary uses:***

*Breast cancer

***Other uses:***

*Health Canada approved indication



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## SPECIAL PRECAUTIONS:

***Caution:***
- ensure blood glucose is optimized prior to initiation of capivasertib[3]; severe ***hyperglycemia***, including fatal cases of diabetic ketoacidosis, has been reported[8]
- capivasertib ***dose reduction*** may be required for drug interactions involving the CYP 3A4 metabolic pathway[3]

***Carcinogenicity:*** Carcinogenicity studies have not been conducted.[3]

***Mutagenicity:*** Not mutagenic in Ames test. Capivasertib was genotoxic in rat bone marrow *in vivo* via aneugenic mechanism, but not in other mammalian *in vivo* chromosome tests.[3]

***Fertility:*** In animal studies, degenerative changes in the testes and epididymides were observed in mice, rats, and dogs at exposures similar to those seen following human clinical exposure and were not reversible during the study period. No effect on fertility was observed in male rats. Female fertility was not studied in animals.[3,5]

***Pregnancy:*** In animal studies, when capivasertib was administered during the period of organogenesis, post-implantation loss, reduced fetal weights, and minor fetal visceral variations were observed at exposures less than those seen following human clinical exposure. Pregnancy tests are recommended prior to starting treatment with capivasertib. For female patients of reproductive potential, contraception is recommended during treatment and for at least 4 weeks after the last dose of capivasertib.[3,5] For male patients with female partners of childbearing potential, contraception is recommended during treatment and for at least 16 weeks after the last dose of capivasertib.[5,7]

***Breastfeeding*** is not recommended due to the potential secretion into breast milk. In animal studies, excretion into milk was demonstrated by confirmed exposure to capivasertib in the suckling pups.[3]

## SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9,10]

**Incidence data in the Side Effects table is based on combination regimen with fulvestrant.**

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | anemia (4%) |
| | leukopenia (32-35%, severe 1%) |
| | lymphopenia (46-49%, severe 10%) |
| gastrointestinal | *emetogenic potential:* low[11] |
| | ***diarrhea*** (67-77%, severe 9-12%); see paragraph following **Side Effects** table |
| | dry mouth (4%) |
| | dyspepsia (3%) |
| | nausea (27-35%, severe 1%) |
| | ***stomatitis*** (16-25%, severe 2%) |
| | vomiting (16-21%, severe 1-2%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| general disorders and administration site conditions | fatigue/asthenia (22-38%, severe 1-2%) |
| | pyrexia (6%, severe <1%) |
| immune system | hypersensitivity (<1%); anaphylactic reactions reported[5] |
| infections and infestations | urinary tract infection (2-14%, severe <1%) |
| investigations | calcium (corrected) decrease (16%, severe <1%) |
| | creatinine increase (3-22%, severe 2%) |
| | ***fasting glucose increase*** (37%, severe 3%); see paragraph following **Side Effects** table |
| | ***random glucose increase*** (57%, severe 11%); see paragraph following **Side Effects** table |
| | sodium decrease (20%, severe 3%) |
| | triglyceride increase (23-30%, severe <1%) |
| metabolism and nutrition | decreased appetite (11-17%, severe <1%) |
| | ***hyperglycemia*** (17%, severe 2%); see paragraph following **Side Effects** table |
| | hypokalemia (18%, severe 3%) |
| nervous system | dysgeusia (6%) |
| | headache (5-17%) |
| renal and urinary | acute kidney injury (1%) |
| | renal injury[5] (11%, severe 3%) |
| skin and subcutaneous tissue | ***cutaneous adverse reactions*** (47-56%, severe 15-17%); see paragraph following **Side Effects** table |

Adapted from standard reference[3,5] unless specified otherwise.

Severe ***hyperglycemia***, including ketoacidosis and diabetic metabolic decompensation, has been reported in patients receiving capivasertib. Some cases have been fatal.[8] Hyperglycemia induced by capivasertib is attributed to its inhibition of the AKT pathway.[3,12] Median time to onset of hyperglycemia is 15 days (range 1 to 367 days)[5]. Diabetic ketoacidosis can occur anytime during treatment with capivasertib, with some cases reported as early as 10 days after initiation of therapy.[8] Safety of capivasertib in patients with Type 1 diabetes, diabetes requiring insulin, or those with a HbA1C greater than 8% has not been established. Hyperglycemia occurs more frequently in patients with a baseline HbA1C of 6.5% or higher compared to those with a baseline HbA1C below 6.5%.[7] Baseline fasting blood glucose and HbA1C testing is recommended to optimize blood glucose levels before starting capivasertib. Monitor fasting blood glucose and HbA1C at regular intervals during treatment. More frequent monitoring of blood glucose levels is recommended in patients with history of diabetes mellitus or risk factors for hyperglycemia. Monitor other metabolic parameters (e.g., blood ketones) as indicated.[3] Management of hyperglycemia may include initiation or intensification of oral anti-diabetic agents (such as metformin) with capivasertib treatment interruption and/or dose reduction. For severe hyperglycemia, consider adding insulin as clinically indicated.[7] Endocrinology consult may be required. Hold capivasertib if signs/symptoms of diabetic ketoacidosis are present. Permanently discontinue capivasertib for life-threatening hyperglycemia or for confirmed diabetic ketoacidosis.[3]

***Diarrhea*** is common with capivasertib and can be severe. Serious complications of diarrhea such as dehydration, hypokalemia, acute kidney injury, and arrhythmia have been reported.[7] Median time to onset for diarrhea is 8 days (range 1-519 days). Increased frequency of diarrhea is reported when metformin is initiated during capivasertib



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treatment. Median time to recovery in patients with grade 2 or higher diarrhea is 4 days (range 1-154).[3,5] Patients are advised to start anti-diarrheal treatment (e.g., loperamide) at the first sign of diarrhea and increase oral fluids. Depending on the severity, capivasertib treatment interruption, dose reduction, or permanent discontinuation may be required to manage diarrhea.[3]

***Cutaneous adverse reactions*** frequently occur with capivasertib and may include maculopapular rash, pruritis, erythema, blisters, drug eruption, dermatitis, eczema, exfoliative dermatitis, purpura, and hyperpigmentation.[3] Erythema multiforme, palmar-plantar erythrodysesthesia, and drug reaction with eosinophilia and systemic symptoms (DRESS) have also been reported. The median time to onset of cutaneous adverse reactions is 12 days (range 1-575 days).[3,5] Management may include emollients, antihistamines, and/or topical or systemic corticosteroids. Early consultation with a dermatologist is recommended. Depending on the severity and duration of reactions, treatment interruption, dose reduction, or permanent discontinuation may be required.[3]

## INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| grapefruit juice[3] | may increase plasma level of capivasertib | may inhibit CYP 3A4 metabolism of capivasertib in the intestinal wall | avoid grapefruit juice during capivasertib treatment |
| metformin[3,13] | based on physiological modelling, no clinically meaningful increase in metformin AUC is predicted | possible inhibition of OCT2, MATE1 and MATE2K by capivasertib | when used concurrently, more frequent blood glucose monitoring is recommended |
| midazolam[3, 7] | 15-77% increase in midazolam AUC | weak inhibition of CYP 3A4 by capivasertib | avoid concurrent use; if unavoidable, monitor for midazolam toxicity and adjust midazolam dose as needed |
| itraconazole[3, 7] | 95% increase in capivasertib AUC and 70% increase in $C_{max}$ | strong inhibition of CYP 3A4 by itraconazole | avoid; if unavoidable, reduce capivasertib dose (e.g., from 400 mg twice daily to 320mg twice daily for 4 consecutive days of each week) and monitor for capivasertib toxicity |
| rabeprazole[3] | not clinically significant; 6% decrease in capivasertib AUC and 27% decrease in $C_{max}$ | pH-dependent solubility of capivasertib | no action required |
| rifampin[3] | predicted: 70% decrease in capivasertib AUC and 60% decrease in $C_{max}$ | strong induction of CYP 3A4 by rifampin | avoid concurrent use |

Capivasertib is a substrate *of* CYP 3A4. ***CYP 3A4 inhibitors*** may increase the plasma concentration of capivasertib. Avoid concurrent use with *moderate* or *strong* CYP 3A4 inhibitors. If coadministration with *moderate* or *strong* CYP 3A4 inhibitors cannot be avoided, reduce capivasertib dose from 400 mg to 320 mg twice daily for 4 days each week and monitor for capivasertib toxicity. If the CYP 3A4 inhibitor is discontinued, the prior dose of capivasertib may be resumed following a washout period equal to 3 elimination half-lives of the inhibitor.[3] ***CYP 3A4 inducers*** may decrease the plasma concentration of capivasertib which may affect treatment outcome. Avoid concurrent use with *moderate* or *strong* CYP3A4 inducers.[3]

Capivasertib is a weak inhibitor of CYP 3A4. If coadministered with a CYP 3A4 substrate of narrow therapeutic index, monitor for toxicity of the substrate. Dose modification of the substrate may be required.[3]



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*In vitro*, capivasertib is an inhibitor of OCT2, MATE1 and MATE2K. Creatinine is a substrate of OCT2, MATE1 and MATE2K, and capivasertib can decrease its renal tubular secretion by inhibiting the renal transporters. Transient increase in serum creatinine may occur without affecting the glomerular function.[3]

*In vitro*, capivasertib inhibits CYP2D6, CYP2C9, UGT1A1 as well as BCRP, OATP1B1, OATP1B3, and OAT3. Also, capivasertib is a substrate of UGT2B7 and P-gp. Clinical significance is unknown.[3]

## SUPPLY AND STORAGE:

***Oral:*** AstraZeneca Canada Inc. supplies capivasertib as 160 mg and 200 mg film-coated tablets. Store at room temperature.[3]

***Additional information***: Capivasertib tablets are packaged in blister cards containing 16 tablets per card. Each carton contains 4 blister cards (equivalent to 4 weeks supply when dispensing usual dose without dose modification).[3]

## DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults***:

BC Cancer usual dose noted in ***bold, italics***

*Oral:*

Cycle Length:
***4 weeks***[2,8,14]:

***400 mg**** (range 200-400 mg) ***PO twice daily for 4 consecutive days starting on day 1*** (followed by 3 consecutive days without treatment). Repeat weekly.

Administer with food or on an empty stomach approximately 12 hours apart.

*dose adjustment may be required for some drug interactions

*Concurrent radiation:* no information found

*Dosage in renal failure:*

CrCl ≥30 mL/min: no dose adjustment required[3]
CrCl <30 mL/min: no information found

calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

*Dosage in hepatic failure* [3]*:*

| Bilirubin | | AST | Dose |
|---|---|---|---|
| ≤1.5xULN | and | any | 100% |
| 1.5-3x ULN | | any | 100%; monitor closely for toxicity |
| >3x ULN | | any | no information found |

*Dosage in dialysis:* no information found



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***Children:*** safety and efficacy have not been established

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