Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Truqap®
Common Name: capivasertib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Piqray	Non-Recommended with Conditions

Pharmacology/Usage: Capivasertib, the active ingredient of Truqap®, is a kinase inhibitor. Capivasertib is an inhibitor of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2, and AKT3) and inhibits phosphorylation of downstream AKT substrates. AKT activation in tumors is a result of activation of upstream signaling pathways, mutations in *AKT1*, loss of phosphatase and tensin homolog (PTEN) function and mutations in the catalytic subunit alpha of phosphatidylinositol 3-kinase (*PIK3CA*).

In vitro, capivasertib reduced growth of breast cancer cell lines including those with relevant *PIK3CA* or *AKT1* mutations or *PTEN* alteration. In vivo, capivasertib alone and in combination with fulvestrant inhibited tumor growth of mouse models including estrogen receptor positive breast cancer models with alterations in *PIK3CA*, *AKT1*, and *PTEN*.

Indication: In combination with fulvestrant, is indicated 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*-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animals and mechanism of action, Truqap® can cause fetal harm when administered to a pregnant woman. There are no available data on the use in pregnant women. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status of females of reproductive potential prior to starting Truqap®. Advise females of reproductive potential to use effective contraception during treatment and for 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 160mg, 200mg.

Swallow tablets whole; Do not chew, crush, or split tablets prior to swallowing. In addition, do not take tablets that are broken, cracked, or otherwise not intact.

Recommended Dosage: Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with Truqap®, based on the presence of one or more of the following genetic alterations in tumor tissue: *PIK3CA/AKT1/PTEN*. Information on FDA-approved tests for the detection of *PIK3CA, AKT1*, and *PTEN* alterations is available at http://www.fda.gov/companiondiagnostics.

Assess fasting blood glucose (FG) and hemoglobin A1C (HbA1c) prior to starting Truqap® and at regular intervals during treatment.

The recommended dosage, in combination with fulvestrant, is 400mg PO BID (about 12 hours apart), with or without food, for 4 days followed by 3 days off. Continue Truqap® until disease progression or unacceptable toxicity. If a patient misses a dose within 4 hours of the scheduled time, instruct the patient to take the missed dose; however, if a patient misses a dose more than 4 hours of the scheduled time, instruct the patient to skip the dose and take the next dose at its usual scheduled time. If a patient vomits a dose, instruct the patient not to take an additional dose and take the next dose at its usual scheduled time.

For premenopausal and perimenopausal women, administer a luteinizing hormone-releasing hormone (LHRH) agonist per current clinical practice standards. For men, consider administering a LHRH agonist per clinical practice standards.

Dosage modifications may be required for adverse reactions, such as hyperglycemia, diarrhea, cutaneous adverse reactions, or other adverse reactions. There is a recommended first dose reduction and second dose reduction; permanently discontinue Truqap® if unable to tolerate the second dose reduction. Refer to the prescribing information for additional information.

Dose modifications are not recommended in patients with mild to moderate renal impairment. Truqap® has not been studied in patients with severe renal impairment. Dose modifications are not recommended for patients with mild hepatic impairment. Monitor patients with moderate hepatic impairment for adverse reactions due to potential increased capivasertib exposure. Truqap® has not been studied in patients with severe hepatic impairment.

Drug Interactions: Capivasertib is a CYP3A substrate. Avoid concomitant use with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce the dose of Truqap® and monitor patients for adverse reactions. When concomitantly used with a moderate CYP3A inhibitor, reduce the dose of Truqap® and monitor for adverse reactions.

Avoid the concomitant use of Truqap® with strong or moderate CYP3A inducers.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Truqap® with fulvestrant) minus reported % incidence for placebo with fulvestrant for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (58%), nausea (21%), stomatitis (20%), vomiting (14%), cutaneous adverse reactions (40%), fatigue (11%), hyperglycemia (14.5%), decreased appetite (9%), headache (4%), urinary tract infection (9%), and renal injury (9.5%).

Laboratory abnormalities included increased random glucose (41%), increased fasting glucose (8%), decreased lymphocytes (35%), decreased hemoglobin (25%), decreased leukocytes (12%), decreased neutrophils (9%), decreased platelets (6%), increased triglycerides (8%), increased alanine aminotransferase (10%), decreased corrected calcium (11%), increased creatinine (14.4%), and decreased potassium (9%).

Severe hyperglycemia, associated with ketoacidosis, occurred in patients treated with Truqap®. The safety of Truqap® has not been established in patients with Type 1 diabetes or diabetes requiring insulin. Hyperglycemia occurred in 18% of patients treated with Truqap®, and dose reduction for hyperglycemia was required in 0.6% of patients and permanent discontinuation was required in 0.6% of patients. The median time to first occurrence of hyperglycemia was 15 days. In the 65 patients with hyperglycemia, 45% required treatment with anti-hyperglycemic medication. Of the 29 patients who required anti-hyperglycemic medication during treatment with Truqap®, 66% remained on these medications at treatment discontinuation or last follow-up. Assess fasting blood glucose and HbA1c, and optimize blood glucose prior to treatment. Inform patients about the potential of Truqap® to cause hyperglycemia. Assess fasting blood glucose at least every 2 weeks during the first month and at least once a month starting from the second month, prior to the scheduled dose of Truqap®. Monitor HbA1c every 3 months. Monitor fasting blood glucose more frequently during Truqap® treatment in patients with a medical history of diabetes and in patients with risk factors for hyperglycemia. If a patient experiences hyperglycemia after starting treatment with

Truqap®, monitor fasting blood glucose as clinically indicated, and at least twice weekly until fasting blood glucose decreases to normal levels.

Severe diarrhea associated with dehydration occurred in patients who received Truqap®. Diarrhea occurred in 72% of patients, and the median time to first occurrence was 8 days. Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start antidiarrheal treatment at the first sign of diarrhea while taking Truqap®.

Cutaneous adverse reactions, which can be severe, including erythema multiforme, palmar-plantar erythrodysesthesia, and drug reaction with eosinophilia and systemic symptoms (DRESS), occurred in patients who received Truqap®. Cutaneous adverse reactions occurred in 58% of patients, and dose reduction was required in 7% of patients while 7% of patients permanently discontinued Truqap® due to cutaneous adverse reactions. The median time to onset of cutaneous adverse reactions was 13 days. Monitor patients for signs and symptoms of cutaneous adverse reactions. Early consultation with a dermatologist is recommended.

Contraindications: In patients with severe hypersensitivity to Truqap® or any of its components.

Manufacturer: AstraZeneca Pharmaceuticals LP.

Analysis: The efficacy of Truqap® with fulvestrant was assessed in a randomized, double-blind, placebo-controlled, multicenter study (CAPItello-291 study) that included adult patients (N=708) with locally advanced (inoperable) or metastatic HR-positive, HER2-negative breast cancer, of which 289 patients had tumors with eligible *PIK3CA/AKT1/PTEN*-alterations. All were required to have progression on an aromatase inhibitor (AI) based treatment in the metastatic setting or recurrence on or within 12 months of completing (neo)adjuvant treatment with an AI. Patients could have received up to two prior lines of endocrine therapy and up to 1 line of chemotherapy for locally advanced (inoperable) or metastatic disease.

Patients were randomized to either 400mg Truqap® (N=355) or placebo (N=353), given PO BID for 4 days, followed by 3 days off treatment each week of 28-day treatment cycle. Fulvestrant 500mg IM injection was administered on cycle 1 days 1 and 15, and then at day 1 of each subsequent 28-day cycle. Patients were treated until disease progression or unacceptable toxicity.

Of the 289 patients whose tumors were *PIK3CA/AKT1/PTEN*-altered, the median age was 59 years (range 34 to 90), while 99% were female, 52% were white, 66% had Eastern Cooperative Oncology Group (ECOG) performance status of 0, 34% had ECOG performance status of 1, and 18% were premenopausal or perimenopausal. Seventy-six percent had an alteration of *PIK3CA*, 13% had an alteration in *AKT1*, and 17% had an alteration in *PTEN*. All patients received prior endocrine-based therapy (100% AI based treatment and 44% received tamoxifen).

The major efficacy outcome was investigator-assessed progression-free survival (PFS) in the overall population and in the population of patients whose tumors have *PIK3CA/AKT1/PTEN*-alterations evaluated per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In addition, overall survival (OS), investigator assessed objective response rate (ORR) and duration of response (DoR) were assessed.

A statistically significant difference in PFS was observed in the overall population and the population of patients whose tumors have *PIK3CA/AKT1/PTEN*-alteration. An exploratory analysis of PFS in the 313 patients (44%) whose tumors did not have a *PIK3CA/AKT1/PTEN*-alteration demonstrated a hazard ratio (HR) of 0.79, indicating that the difference in the overall population was mainly attributed to the results seen in the population of patients whose tumors have *PIK3CA/AKT1/PTEN*-alteration. Efficacy results for patients with *PIK3CA/AKT1/PTEN*-altered tumors are presented in the table below, which was adapted from the prescribing information. Results from the blinded independent review committee assessment were consistent with the investigator assessed PFS results. Overall survival results were immature at the time of the PFS analysis (30% of the patients died).

	Truqap® with fulvestrant (N=155)	Placebo with fulvestrant (N=134)
Investigator-Assessed Progression-Free Survival (PFS)		
Number of events (%)	121 (78%)	115 (86%)
Median, months	7.3	3.1
HR; p-value	0.50; p<0.0001	
Investigator-Assessed confirmed Objective Response Rate (ORR)		
Patients with measurable disease	132	124
ORR	26%	8%
Complete response rate	2.3%	0%
Partial response rate	23%	8%
Median DoR, months	10.2	8.6

Place in Therapy: Truqap® is an oral kinase inhibitor indicated, 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 as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. Assess fasting blood glucose and hemoglobin A1c prior to starting Truqap® and at regular intervals during treatment. The safety and efficacy of Truqap® were assessed in a multicenter, randomized, double-blind, placebo-controlled study that included adult patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer. The major efficacy outcome was investigator-assessed PFS in the overall population, and in the population of patients whose tumors have *PIK3CA/AKT1/PTEN*-alterations per RECIST, version 1.1. Results suggested that a statistically significant difference in PFS was observed in the overall population and the population of patients whose tumors have *PIK3CA/AKT1/PTEN*-alteration (HR 0.50, p<0.0001 in patients with *PIK3CA/AKT1/PTEN*-altered tumors), in favor of Truqap® with fulvestrant as compared to placebo with fulvestrant.

It is recommended that Truqap® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Truqap [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.