

Policy Type: PA/SP

Pharmacy Coverage Policy: EOCCO230

Description

Tivozanib (Fotivda) is an orally administered VEGFR kinase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tivozanib (Fotivda)	1.34 mg capsules	Relapsed or refractory advanced renal cell carcinoma, following at least two prior systemic therapies	21 capsules/28 days
	0.89 mg capsules		

Initial Evaluation

- I. **Tivozanib (Fotivda)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Not used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
 - D. A diagnosis of **advanced or metastatic renal cell carcinoma** when the following are met:
 1. Provider attestation the member has clear cell component histology; **AND**
 2. Member has renal cell carcinoma that is relapsed or refractory to at least **TWO** prior systemic therapies (e.g., axitinib [Inlyta], ipilimumab [Yervoy], nivolumab [Opdivo], everolimus [Afinitor]; **AND**
 - i. At least **ONE** of the prior therapies is an anti-VEGFR TKI (e.g., axitinib [Inlyta], lenvatinib [Lenvima], pazopanib [Votrient], sunitinib [Sutent], cabozantinib [Cabometyx]).

- II. Tivozanib (Fotivda) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Renal cell carcinoma prior to third-line treatment

- III. Tivozanib (Fotivda) is considered investigational when used for all other conditions, including but not limited to:
- A. Renal cell carcinoma in combination with other oncolytic therapies
 - B. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
 - C. Prostate cancer
 - D. Breast cancer
 - E. Ovarian, fallopian tube, or primary peritoneal cancer
 - F. Lung Cancer
 - G. Gastrointestinal tumors
 - H. Hepatocellular carcinoma
 - I. Cholangiocarcinoma
 - J. Colorectal cancer
 - K. Glioblastoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Provider attestation the medication will not be used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
- IV. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

- I. Tivozanib (Fotivda) is a VEGFR tyrosine kinase inhibitor (TKI) that is FDA-approved for patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more systemic therapies. Tivozanib (Fotivda) is approved for 21 days on therapy and seven days off until disease progression or unacceptable toxicity. It is the first therapy specifically FDA-approved for the third-line setting, but joins several other anti-VEGFR medications for this condition, as well as immunotherapies and mTOR inhibitors. All therapy categories are utilized in the subsequent treatment setting after members have progressive disease.

- II. Other anti-VEGFR medications include: cabozantinib (Cabometyx), pazopanib (Votrient), sorafenib (Nexavar), lenvatinib (Lenvima), sunitinib (Sutent) and axitinib (Inlyta). Immunotherapy options include: ipilimumab (Yervoy), nivolumab (Opdivo), avelumab (Bavencio). The mTOR inhibitors include therapies such as everolimus (Afinitor), temsirolimus (Torisel). Often, immunotherapies will be used in combination with each other, or in combination with anti-VEGFR medications. The mTOR inhibitors are also utilized in combination with anti-VEGFR medications; however, use of two concomitant anti-VEGFR medications has not been evaluated, and given the unfavorable safety profiles of these medications, combination treatment is not advised.
- III. As of March 2021, all three categories of medications are used for clear cell RCC. In the subsequent treatment setting, NCCN Cat. 1 recommended regimens include cabozantinib (Cabometyx), nivolumab (Opdivo), axitinib (Inlyta), and lenvatinib (Lenvima) plus everolimus (Afinitor). The remainder have Cat. 2A recommendations, with the exception of sorafenib (Nexavar) which has a Cat. 2B recommendation.
- IV. Treatment choice is based on stage of disease, prognosis, line of therapy, and other patient characteristics. Tolerability and safety considerations are taken into account for treatment choice as well. Given the extensive treatment options, combinations, and unfavorable safety profiles that require extensive medication monitoring, medication should be prescribed by or in consultation with a specialist.
- V. In 2013 tivozanib (Fotivda) was evaluated in a Phase 3 trial vs. sorafenib (Nexavar) in 517 patients with RCC for initial targeted therapy in those that had received up to one prior systemic treatment. Patients had prior nephrectomy, clear cell RCC, and up to one prior therapy that was not an anti-VEGFR. Progression-free survival (PFS) was statistically significant favoring tivozanib (Fotivda); however, the overall survival (OS) was not statistically different. In 2013, the FDA issued a Complete Response Letter to Aveo, given an inconclusive risk benefit assessment and required another trial from the manufacturer in the advanced setting.
- VI. Following the CRL, tivozanib (Fotivda) was evaluated in an open-label, randomized, Phase 3 trial vs. sorafenib (Nexavar) in 350 adults with RCC. Ninety-eight percent of patients had clear cell histology. Patients had advanced disease and were relapsed or refractory to two or three prior systemic therapies, including at least one anti-VEGFR therapy. Forty-five percent of patients had two prior anti-VEGFR therapies and 26% had prior checkpoint inhibitor therapy. About 60% of patients had intermediate, 20% had favorable, and 20% had poor prognoses. The study showed a statistical increase in PFS (5.6 months vs. 3.9 months), as well as partial responses (18% vs. 8%); however, OS was not statistically different and numerically favored sorafenib (Nexavar). To date, tivozanib (Fotivda) has not proven to have clinically meaningful outcomes such as increased survival, improvement in quality of life or symptom control. This is similar for the comparator, sorafenib (Nexavar). Thus, clinical benefit of either therapy remains unclear.
- VII. To date, the safety tivozanib (Fotivda) is similar to other anti-VEGFR medications. Serious adverse events (AE) occurred in 11% of patients on tivozanib (Fotivda) and in 10% for sorafenib

(Nexavar). AE more frequent with tivozanib (Fotivda): hypertension (44% vs. 31%), bleeding (17% vs. 12%), nausea (30% vs. 18%), decreased appetite (39% vs. 30%), dysphonia (27% vs. 9%), cough (22% vs. 15%), and hypothyroidism (24% vs. 11%). AE more frequent with sorafenib (Nexavar): diarrhea (54% vs. 44%), rash (52% vs. 18%), and palmar-plantar syndrome (41% vs. 16%). Stomatitis, vomiting, pain, dyspnea, and weight loss were common and occurred in similar rates between treatment arms

- VIII. Dose interruption due to AE occurred in 48% of the tivozanib (Fotivda) group and 63% of the sorafenib (Nexavar) group. Dose reductions due to AE occurred in 24% for tivozanib (Fotivda) and 38% for sorafenib (Nexavar). The lower dose reduction and interruption rates for tivozanib (Fotivda) are likely attributable to the seven-day break within each cycle vs. continuous dosing with sorafenib (Nexavar). Given lack of long-term safety evaluation and lack of evaluation against placebo, true benefits and harms are unknown at this time. At this time there is insufficient safety information (given limited patient experience and duration of therapy) to definitively indicate that there is substantial safety differences between any of the anti-VEGFR therapies.

Investigational or Not Medically Necessary Uses

- I. Tivozanib (Fotivda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Renal cell carcinoma prior to third-line.
 - i. Tivozanib (Fotivda) has been evaluated for first-line and second-line treatment but did not achieve FDA-approval given uncertain risks and benefits.
 - B. The following indications have not been sufficiently studied for efficacy and use outside of clinical trials is not advised given the unfavorable safety profile alone or in combination with other medications:
 - i. Renal cell carcinoma in combination with other oncolytic therapies
 - ii. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
 - iii. Prostate cancer
 - iv. Breast cancer
 - v. Ovarian, fallopian tube, or primary peritoneal cancer
 - vi. Lung Cancer
 - vii. Gastrointestinal tumors
 - viii. Hepatocellular carcinoma
 - ix. Cholangiocarcinoma
 - x. Colorectal cancer
 - xi. Glioblastoma

References

1. Fotivda [Prescribing Information]. Aveo Pharmaceuticals Inc. Boston, MA. March 2021.
2. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomized, controlled, open-label study. *Lancet Oncol.* 2020;21(1):95-104.
3. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol.* 2013;31(30):3791-3799.
4. NCCN Guidelines for the Treatment of Kidney Cancer. V.2.2021. Updates February 3, 2021.
5. Powles T, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021;32(3):422-423

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021