PDL DRUG REVIEW

Proprietary Name: Fotivda®
Common Name: tivozanib
PDL Category: Antineoplastics

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

Summary

Pharmacology/Usage: Tivozanib, the active ingredient of Fotivda®, is a tyrosine kinase inhibitor. In vitro cellular kinase assays demonstrated that tivozanib inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 and inhibits other kinases. In animal models, tivozanib inhibited angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human renal cell carcinoma.

Indication: For the treatment of adults with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animal studies and its mechanism of action, Fotivda® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant woman to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status of females of reproductive potential prior to starting treatment and advise this population to use effective contraception during treatment with Fotivda® and for one month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Fotivda® and for one month after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 0.89mg, 1.34mg. Do not open capsules.

Fotivda® 0.89mg capsules contain FD&C Yellow No. 5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin sensitivity.

Recommended Dosage: Take 1.34mg PO QD for 21 days on treatment followed by 7 days off treatment for a 28-day cycle. Continue treatment until disease progression or until unacceptable toxicity occurs. Swallow capsules whole with a glass of water. If a dose is missed, the next dose should be taken at the next scheduled time. Do not take 2 doses at the same time.

Initiate medical management for diarrhea, nausea, or vomiting prior to dose interruption or reduction. Dose modifications may be required for adverse reactions, such as hypertension, cardiac failure, arterial thromboembolic events, hemorrhagic events, proteinuria, reverse posterior leukoencephalopathy syndrome, or other adverse reactions. Refer to the prescribing information for further details.

Dose modifications are not required with mild to severe renal impairment; however, the recommended dosage for patients with end-stage renal disease has not been established. While no dose modification is recommended with mild hepatic impairment, reduce the Fotivda® dosage in patients with moderate hepatic impairment to 0.89mg PO QD for 21 days on treatment followed by 7 days off treatment for a 28-day cycle. The recommended dosage for patients with severe hepatic impairment has not been established.

Drug Interactions: Concomitant use of Fotivda® with a strong CYP3A inducer decreases tivozanib exposure, which may reduce Fotivda® anti-tumor activity. Avoid concomitant use of strong CYP3A inducers with Fotivda®.

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 (Fotivda®) minus reported % incidence for sorafenib for all grades. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included fatigue (19%), hypertension (13%), bleeding (5%), diarrhea (0%), nausea (12%), stomatitis (0%), vomiting (1%), decreased appetite (9%), dysphonia (18%), cough (7%), dyspnea (4%), hypothyroidism (13%), back pain (3%), rash (0%), Palmar-plantar erythrodysesthesia syndrome (0%), and weight decreased (0%). Select laboratory abnormalities included lymphocytes decreased (0%), hemoglobin increased (11%), platelets decreased (1%), hemoglobin decreased (0%), creatinine increased (13%), glucose increased (10%), phosphate decreased (0%), sodium decreased (6%), lipase increased (0%), ALT increased (1%), alkaline phosphatase increased (0%), AST increased (0%), potassium increased (3%), magnesium decreased (3%), amylase increased (0%), calcium increased (8%), bilirubin increased (0%), and activated partial thromboplastin time prolonged (8%).

Fotivda® can cause severe hypertension and hypertensive crisis. The median time to onset of hypertension was 2 weeks. Fotivda® has not been studied in patients with systolic BP >150mmHg or diastolic BP >100mmHg. Control blood pressure prior to treatment with Fotivda®. Monitor BP after 2 weeks and at least monthly thereafter during treatment with Fotivda®. Treat patients with anti-hypertensive therapy when hypertension occurs during treatment with Fotivda®. Withhold treatment for severe hypertension despite optimal anti-hypertensive therapy. For persistent hypertension despite use of anti-hypertensive medications, reduce the Fotivda® dose. If Fotivda® is interrupted, monitor patients receiving anti-hypertensive treatments for hypotension.

Fotivda® can cause serious, sometimes fatal, cardiac failure. Fotivda® has not been studied in patients with symptomatic cardiac failure within the preceding 6 months before Fotivda® treatment initiation. Periodically monitor patients for symptoms of cardiac failure throughout treatment with Fotivda®.

Fotivda® can cause serious, sometimes fatal, cardiac ischemia and arterial thromboembolic events. Fotivda® has not been studied in patients who had an arterial thromboembolic event, MI, or unstable angina within the preceding 6 months before Fotivda® treatment initiation. Closely monitor patients who are at risk for, or who have a history of these events during treatment with Fotivda®.

Fotivda® can cause serious, sometimes fatal, venous thromboembolic events. Closely monitor patients who are at risk for, or who have a history of these events during treatment with Fotivda®.

Fotivda® can cause serious, sometimes fatal, hemorrhagic events. Fotivda® has not been studied in patients with significant bleeding within the preceding 6 months before Fotivda® treatment initiation. Closely monitor patients who are at risk for or who have a history of bleeding during treatment with Fotivda®.

Fotivda® can cause proteinuria. Of the patients who developed proteinuria, 3.7% (N=3/81) had acute kidney injury either concurrently or later during treatment. Monitor patients for proteinuria before initiation of, and periodically throughout, treatment with Fotivda®. For patients who develop moderate to severe proteinuria, reduce the dose or interrupt treatment. Discontinue treatment in patients who develop nephrotic syndrome.

Fotivda® can cause thyroid dysfunction. Monitor thyroid function before initiation of, and periodically throughout treatment with Fotivda®. Treat hypothyroidism and hyperthyroidism to maintain euthyroid state before and during treatment with Fotivda®.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway, such as Fotivda®. Thus, Fotivda® has the potential to adversely affect wound healing. Withhold Fotivda® for at least 24 days prior to elective surgery, and do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Fotivda® after resolution of wound healing complications has not been established.

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by MRI, can occur with Fotivda®. Perform an evaluation of RPLS in any patient presenting with seizures, headaches, visual disturbances, confusion, or altered mental state. Discontinue Fotivda® in patients who develop RPLS.

Contraindications: There are no contraindications listed with this product.

Manufacturer: AVEO Pharmaceuticals, Inc

Analysis: The safety and efficacy of Fotivda® were assessed in TIVO-3, a multicenter, randomized, open-label study that compared Fotivda® with sorafenib in patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments, including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib. Treatment was continued until disease progression or unacceptable toxicity.

The median age of included adults was 63 years (range 30 to 90 years), while 73% were male, 95% were Caucasian, 48% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 49% had an ECOG PS of 1, and 98% had clear cell or clear cell component histology. Prior therapy included 2 kinase inhibitors (45%), a kinase inhibitor plus an immune checkpoint inhibitor (26%), and a kinase inhibitor plus another systemic agent (29%). At the time of study entry, 20% of patients had favorable, 61% intermediate, and 19% poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognoses.

The primary efficacy outcome measure was progression-free survival (PFS) assessed by a blinded independent radiology review committee. Other efficacy endpoints were objective response rate (ORR) and overall survival (OS). Results can be seen in the table below, which was adapted from the prescribing information.

	Fotivda® (N=175)	Sorafenib (N=175)
Progression Free Survival (PFS)		
Events, n (%)	123 (70%)	123 (70%)
Progressive Disease	103 (59%)	109 (62%)
Death	20 (11%)	14 (8%)
Median, months	5.6	3.9
Hazard Ratio (HR); p-value	0.73; p=0.016	
Overall Survival		
Deaths, n (%)	125 (71%)	126 (72%)
Median, months	16.4	19.2
HR	0.97	
Objective Response Rate (ORR)		

	Fotivda® (N=175)	Sorafenib (N=175)
ORR, %	18%	8%
Median duration of response in months	Not estimable	5.7

Place in Therapy: Fotivda®, an oral tyrosine kinase inhibitor, is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies. In an open-label study compared with sorafenib, Fotivda® was more effective than sorafenib for the primary endpoint of progression free survival (p=0.016); however, overall survival was not significantly different.

In a 2020 network meta-analysis by Manz et al[2], the safety and efficacy of approved first-line tyrosine kinase inhibitors were assessed for the treatment of metastatic renal cell carcinoma. The authors concluded that while cabozantinib, sunitinib, pazopanib, and tivozanib did not differ significantly in efficacy (sorafenib was associated with a significantly shorter PFS when indirectly compared with cabozantinib), tivozanib was associated with a more favorable safety profile regarding grade 3 or 4 toxicities.

It is recommended that Fotivda® 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] Fotivda [package insert]. Boston, MA: AVEO Pharmaceuticals; 2021.
[2] Manz KM, Fenchel K, Eilers A, et al. Efficacy and safety of approved first-line tyrosine kinase inhibitor treatments in metastatic renal cell carcinoma: A network meta-analysis. Adv Ther. 2020; 37(2): 730-744.