NEW DRUG APPROVAL

Brand Name	Fotivda®
Generic Name	tivozanib hydrochloride
Drug Manufacturer	AVEO Pharmaceuticals, Inc.

New Drug Approval

FDA Approval Date: March 10, 2021

Review Designation: Standard

Type of Review: Type 1 - New Molecular Entity, New Drug Application (NDA) 212094

Dispensing Restrictions: Specialty Primarily, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Kidney cancer is an abnormal growth of cells in one or both kidneys. The kidneys filter waste from your blood and produce urine. Kidney cancer may spread to other parts of your body. This type of cancer may also be called renal cell carcinoma. Renal cell carcinoma (RCC) is an insidious neoplasm, accounting for approximately 2% of global cancer diagnoses and deaths and projected to increase in burden worldwide. Cancers of the kidney and renal pelvis have rapidly become more common in the developed world over the past decades, more than doubling in incidence in the United States (US) since 1975.

RCC is more common in older men and minorities in the US, where significant racial disparities persist in RCC survival. Modifiable risk factors such as smoking, obesity, uncontrolled hypertension, poor diet and occupational exposure are prime candidates for prevention efforts in the campaign against this aggressive cancer.

After more than two decades of rising rates, in recent years the total kidney cancer incidence worldwide has shown signs of stabilizing, or even decreasing. In adults, kidney cancer consists of renal cell carcinoma (RCC), the predominant form, and renal transitional cell carcinoma (RTCC); these types primarily arise in the renal parenchyma and renal pelvis, respectively. In the United States, there are approximately 73,750 new cases per year and almost 14,830 deaths each year from RCC. It occurs more commonly in men (twofold in men compared with women) and usually in the sixth to eighth decade of life, with a median age of 64 years. The 5-year survival rate for patients with advanced disease is 13%.

Efficacy

The efficacy of Fotivda® was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open label, multicenter trial of Fotivda® versus 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.

Table 1. TIVO-3 (NCT02627963): Randomized, Open-Label Trial of Fotivda Versus Nexavar (sorafenib)	
Study Population	• 350 patients with R/R advanced RCC • Must have received 2 or 3 prior systemic treatments, including at least one VEGFR tyrosine kinase inhibitor (TKI) other than Nexavar or Fotivda • Median age: 62 years (range, 30 to 90 years) • 73% male • 95% Caucasian • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Prior therapy included 2 TKIs (45%), a TKI plus an immune checkpoint inhibitor (26%), and a TKI plus another agent (29%)
Interventions	Patients were randomized to receive Fotivda 1.34 mg orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle, or to receive sorafenib 400 mg orally twice a day continuously, until disease progression or unacceptable toxicity.
Endpoints	• Primary outcome: progression-free survival (PFS) • Secondary outcomes: objective response rate, overall survival (OS), and duration of response
Efficacy and Safety Results	• OS: 16.4 months for Fotivda vs. 19.2 months for Nexavar • PFS (median months): 5.6 for Fotivda vs. 3.9 for Nexavar • Objective response rate: 18% for Fotivda vs. 8% for Nexavar • Adverse events were found in 84% of patients receiving Fotivda and 94% of those receiving Nexavar. • Serious adverse drug events (ADEs) were found in 11% of patients receiving Fotivda and 10% of those receiving Nexavar. • The most common grade 3 or 4 ADE was hypertension, found in 21% of patients receiving Fotivda and 14% of those receiving Nexavar.

Sources: Fotivda Prescribing Information, NCT02627963

Safety

ADVERSE EVENTS

The most common (≥20%) adverse reactions were fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis, and the most common Grade 3 or 4 laboratory abnormalities (≥5%) were sodium decreased, lipase increased, and phosphate decreased.

WARNINGS & PRECAUTIONS

- Hypertension and hypertensive crisis
- Cardiac failure
- Cardia ischemia, arterial thromboembolic events, and venous thrombotic events
- Hemorrhagic events
- Proteinuria
- Thyroid dysfunction
- Embryo-fetal toxicity
- Reversible posterior leukoencephalopathy

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Tivozanib is a potent and selective vascular endothelial growth factor receptor (VEGFR) inhibitor. Tivozanib inhibits phosphorylation of VEGFR-1, VEGFR-2, and VEGFR-3; it also inhibits other kinases (including c-kit and PDGFR β). Tivozanib inhibits angiogenesis, vascular permeability, and tumor growth of various tumor cell types.

Dose & Administration

ADULTS

1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity or disease progression.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

- Mild to severe renal impairment (CrCl 15 to 89 mL/min): No dosage adjustment is necessary.
- End-stage renal disease: The recommended dosage has not been established.

HEPATIC IMPAIRMENT

- Mild hepatic impairment (total bilirubin at the upper limit of normal (ULN) or less with AST greater than ULN; or total bilirubin 1.1 to 1.5 times ULN with any AST): No dosage adjustment is necessary.
- Moderate hepatic impairment (total bilirubin 1.6 to 3 times ULN with any AST): Reduce the dose of tivozanib to 0.89 mg PO once daily for 21 days, followed by 7 days off treatment, every 28 days.
- Severe hepatic impairment (total bilirubin 3.1 to 10 times ULN with any AST): The recommended dosage of tivozanib has not been established.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 1.34 mg and 0.89 mg