Tivozanib (Fotivda)
National Drug Monograph
June 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Tyrosine kinase inhibitor that inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3; also inhibits other kinases including c-kit and PDGFR-β at clinically relevant concentrations
- Inhibition of VEGFR and other kinases leads to inhibition of angiogenesis, vascular permeability, and tumor growth

Indication(s) Under Review in This Document

- Renal cell carcinoma (RCC), advanced, relapsed or refractory following two or more prior systemic therapies

Dosage Form(s) Under Review

- *Capsule, oral, as hydrochloride:
  - Fotivda: 0.89mg
  - Fotivda: 1.34mg
- Dosing Schedule: days 1 to 21 of a 28-day cycle
- *Each tivozanib 1.34 mg capsule contains 1.5 mg of tivozanib hydrochloride with inactive ingredients. Each tivozanib 0.89 mg capsule contains 1.0 mg of tivozanib hydrochloride with inactive ingredients.

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of tivozanib was evaluated in TIVO-3, a phase III, multi-center trial comparing tivozanib to sorafenib in patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic therapies including at least one VEGFR inhibitor other than sorafenib or tivozanib. This trial demonstrated a progression-free survival (PFS) benefit leading to FDA approval.
- Efficacy data are summarized in Table 1.

Table 1: Efficacy results from clinical trials

Study	Design	Results (N=350)	Comments
TIVO-3 Trial	Phase 3, randomized, open-label, controlled, multicenter trial **Inclusion**: Age ≥18, metastatic RCC with a clear cell component, previous unsuccessful treatment with 2 or 3 systemic regimens (1 of which were VEGFR inhibitors other	**Primary**: PFS **Secondary**: overall survival (OS), proportion of patients who achieved objective response, duration of response (DOR), and safety Tivozanib 1.5mg orally once daily on Days 1-21 of 28-day cycle (N=175) vs. sorafenib 400mg orally twice daily continuously (N=175)	Subgroup analyses showed statistically significant PFS benefit maintained in patients with

	than tivozanib or sorafenib), ECOG PS 0 or 1 **Exclusion**: Received previous treatment with tivozanib or sorafenib or more than 3 previous regimens for metastatic RCC, active or untreated CNS metastatic disease, inadequate bone marrow function, significant cardiovascular disease, history of acute coronary syndrome or thromboembolic or vascular disorders within 6 mo of study enrollment; non-healing wound	Median age 63, male 73%, Caucasian 95% **IMDC Risk**: Favorable 19% vs. 21%, Intermediate 62% vs. 60%, Poor 18% vs. 19% **Previous therapies**: Two VEGFR inhibitors 45% vs. 46%, Checkpoint inhibitor + VEGFR inhibitor 27% vs. 25%, VEGFR inhibitor + other 28% vs. 29% Median follow-up 19 mo **PFS**: 5.6 mo vs. 3.9 mo (by IRC); HR 0.73 (95% CI 0.56-0.94) **1-yr PFS:** 28% vs. 11% **2-yr PFS:** 18% vs. 5% **OS**: 16.4 mo vs. 19.7 mo; HR 0.99 (95% CI 0.76-1.29) **Objective response:** 18% vs. 8% **DOR**: NR vs. 5.7 mo	IMDC risk of favorable or intermediate, and those with 2 previous VEGFR inhibitors and checkpoint inhibitor + VEGFR inhibitors

IIT=intention-to-treat ; IMDC = international metastatic RCC database consortium, IRC = independent review committee

- The purpose of the TIVO-3 trial was to evaluate the efficacy and safety of tivozanib compared to sorafenib as third- or fourth-line therapy in metastatic RCC with clear cell component.
- The population represented was predominantly intermediate IMDC risk after two prior VEGFR inhibitors.
- Tivozanib demonstrated a statistically significant improvement in PFS and objective response. The PFS benefit was maintained in the favorable and intermediate risk subgroups, HR 0.46 (95% CI 0.25-0.85) and HR 0.69 (95% CI 0.49-0.95) respectively.
- At the time of publication, the median OS difference was not statistically significant. **Final results** were reported in a later publication, showing no difference between tivozanib vs. sorafenib in median OS 16.4 mo vs. 19.2 mo (HR 0.97, 95% CI 0.75-1.24). This was consistent in the subgroup with checkpoint inhibitor therapies alone or in combination (HR 0.84, 95% CI 0.50-1.40).
- Tivozanib was initially compared to sorafenib in the first-line setting of mRCC with clear cell component in the TIVO-1 trial. Median PFS 11.9 mo vs. 9.1 mo (HR 0.797; 95% CI 0.639-0.993), but median OS 29.3 mo vs. 28.8 mo (HR 1.245; 95% CI 0.954-1.625) showed trend towards improved OS with sorafenib. Thus, tivozanib was not approved by the FDA for use in the first-line setting.

Safety Results from Clinical Trials:

- The safety of tivozanib was evaluated in the TIVO-3 trial, compared to sorafenib in third- or fourth-line therapy for metastatic RCC. Among 343 patients who were randomized to receive tivozanib (N=173) or sorafenib (N=170), duration of exposure was 197 days with tivozanib and 141 days with sorafenib.
- Note: No treatment-related adverse events leading to death in either group.
- Summary of safety data from TIVO-3 in ≥15%– refer to Table 2.

Table 2: Safety results from clinical trial

Study	Results (N=343)	Tivozanib vs. Sorafenib
TIVO-3 Trial	AE reported, any grade	Occurred in 99% vs. 100% Most common: Fatigue 67% vs. 48%, hypertension 44% vs. 31%, diarrhea 43% vs. 54%, decreased appetite 39% vs. 30%
	AE reported, grade 3 or 4	Occurred in 67% vs. 72%. Most common: Hypertension 24% vs. 17%, fatigue 13% vs. 12%
	Treatment-related AE, any grade	Occurred in 84% vs. 94%
	Treatment-related AE, grade 3 or 4	Most common: Hypertension 20% vs. 14%
	AE leading to permanent discontinuation	Most common: Malignant neoplasm progression 3% vs. 1%, fatigue 1% vs. 4%
	AE leading to dose interruption/reduction	Interruption: Occurred in 48% vs. 63% Reduction: Occurred in 24% vs. 38%

Safety Considerations

- **Boxed warnings:**
  - None listed
- **Contraindications:**
  - None listed
- **Other warnings / precautions**:
  - **Hypertension**: Common (45%), including grade ≥ 3 events in 22%. Median time to onset was 2 weeks. Hypertensive crisis (including 1 fatality) reported in a small number of patients. Has not been studied in patients with systolic BP >150 mmHg or diastolic BP >100 mmHg.
  - **Cardiac effects:** Cardiac ischemia (3.2%), including grade ≥ 3 events in 1.5% and 0.4% fatal. Cardiac failure (1.6%), including grade ≥3 events in 1% and 0.6% fatal. Has not been studied in patients with symptomatic cardiac failure within the 6 months prior to tivozanib therapy.
  - **Hemorrhage:** Hemorrhage (11% to 17%), including grade 3/4 events in 3%. Has not been studied in patients with significant bleeding within the 6 months prior to tivozanib therapy.
  - **Nephrotoxicity**: Proteinuria (8%), including grade 3 events in 2%. Of those who developed proteinuria, 3.7% had acute kidney injuries either concurrently or later during treatment.
  - **Reversible posterior leukoencephalopathy syndrome (RPLS):** Frequency of reports not specified. Should be evaluated by MRI imaging if patients present with seizures, headaches, visual disturbances, confusion, or altered mental function.
  - **Thromboembolism:** Arterial and venous thromboembolism (2%), including those leading to fatalities. Has not been studied in patients with arterial thrombotic event, myocardial infarction, or unstable angina within the 6 months prior to tivozanib therapy.
  - **Thyroid disorders:** Hypothyroidism (24%) and hyperthyroidism (1%), including grade 3/4 hypothyroidism events in 1%.
  - **Wound healing complications:** May occur with medications that inhibit vascular endothelial growth factor signaling such as tivozanib, though no reported events in clinical trials.
  - **Yellow dye:** Contains FD&C Yellow No. 5 (tartrazine) which can cause allergic-type reactions (including bronchial asthma). More commonly seen in patients who have aspirin hypersensitivity.
  - **Embryo-fetal toxicity**
- **Adverse reactions:**
  - **Common (≥ 30%):** Fatigue (67%), hypertension (44%), diarrhea (43%), decreased appetite (39%), nausea (30%)
  - **Serious (≥ 10%):** Hypertension (24%), fatigue (13%)

Other Considerations

- **Reproductive Considerations**
  - Verify pregnancy status prior to treatment. Patients of childbearing potential or patients with partners who may become pregnant should use effective contraception during therapy and for 1 month after the last dose of tivozanib.
  - Based on mechanism of action and data from animal reproduction studies, in utero exposure to tivozanib may cause fetal harm.
- **Breastfeeding Considerations**
  - It is not known if tivozanib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for 1 month after the last dose of tivozanib.
- **Special Populations**
  - Geriatric use – Of the 1008 patients with advanced RCC treated with tivozanib, 29% were age ≥ 65. No overall differences in safety were observed when compared to those age <65.
  - Renal impairment – No dose modifications are recommended for patients with mild to severe renal impairment (CrCl 15-89 mL/min). Recommended dosage for patients with end-stage renal disease (CrCl <15 mL/min) has not been established.
  - Hepatic impairment – No dose modifications re recommended for patients with mild hepatic impairment (total bilirubin < ULN with AST >ULN or total bilirubin >1-1.5x ULN with any AST). Reduce dose for patients with moderate hepatic impairment (total bilirubin >1.5-3x ULN with any AST). Recommended dosage for patients with severe hepatic impairment (total bilirubin >3-10x ULN with any AST) has not been established.
- **Emetogenic Risk**
  - Minimal or low (<30%)
- **Hepatitis B Virus Screening**
  - Consider obtaining Hepatitis B screening prior to tivozanib due to risk of HBV infection reactivation with start of anti-cancer agent, though this should not delay treatment.
- **Drug Interactions**
  - Avoid concomitant use of strong CYP3A4 inducers, as this can reduce tivozanib anti-tumor activity. Monitor for decreased tivozanib effect if used with moderate CYP3A4 inducers.
- **Guidelines**
  - NCCN Guidelines Version 4.2022 list tivozanib under "Other Recommended Regimens" for subsequent therapy for relapsed or stage IV kidney cancer of clear cell histology after ≥2 prior systemic therapies

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** PFS 5.6 mo vs. 3.9 mo
- **Effect Size:** HR 0.73 (95% CI 0.56-0.94); P=0.016 for PFS
- **Potential Harms (≥ 20%):** moderate
- **Net Clinical Benefit:** moderate

Other Therapeutic Options

There are other regimens that have been evaluated for metastatic RCC that is relapsed after at least 1 prior systemic therapy regimen. The trial data which led to national guideline recommendations for the regimens in the subsequent-line setting after at least 1 prior VEGFR inhibitor regimen are detailed below in table 3.

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Tivozanib **Rino et al 2019** **Pal et al 2019**	TBD	• Advanced or metastatic RCC with clear cell component, relapsed to ≥ 2 systemic therapy regimens • NCCN: Category 2A	• Oral • ECOG PS 0-1 • Tivozanib (N=238) vs. sorafenib (N=234) • Median follow-up: 19 mo for PFS • OS: 16.4 mo vs. 19.2 mo (not statistically significant) • PFS: 5.6 mo vs. 3.9 mo • ORR: 18% vs. 8%
Lenvatinib/everolimus **Motzer et al 2016** **Motzer et al 2015**	F	• Advanced or metastatic RCC with clear cell component, relapsed to ≥ 1 VEGFR-targeted TKI with progression with 9 mo of treatment • NCCN: Category 1	• Oral • ECOG PS 0-1 • Lenvatinib/everolimus (N=51) vs. everolimus (N=50) vs. lenvatinib (N=52) • Median follow-up: 17-19 mo • OS: 25.5 mo vs. 15.4 mo vs. 19.1 mo (only lenvatinib/everolimus vs. everolimus statistically significant) • PFS: 14.6 mo vs. 5.5 mo vs. 7.4 mo (only lenvatinib/everolimus vs. everolimus statistically significant) • ORR: 43% vs. 6% vs. 27%
Nivolumab **CheckMate 025 Trial** **Motzer et al 2015**	F	• Advanced or metastatic RCC with clear cell component, received 1-2 prior anti-angiogenic therapies except mTOR inhibitors • NCCN: Category 1	• Intravenous • Karnofsky PS ≥ 70% • Nivolumab (N=406) vs. everolimus (N=397) • Median follow-up: minimum 14 mo • OS: 25.0 mo vs. 19.6 mo • PFS: 4.6 mo vs. 4.4 mo (not statistically significant) • ORR: 25% vs. 5%
Cabozantinib **METEOR Trial** **Motzer et al 2018** **Choueiri et al 2016** **Choueiri et al 2015**	NF	• Advanced or metastatic RCC with clear cell component; received ≥ 1 prior VEGFR-targeted TKI with progression within 6 mo of treatment • NCCN: Category 1	• Oral • Karnofsky PS ≥ 70% • Cabozantinib (N=330) vs. everolimus (N=328) • Median follow-up: 22 mo for OS; 19 mo for PFS and ORR • OS: 21.4 mo vs. 17.1 mo • PFS: 7.4 mo vs. 3.9 mo • ORR: 17% vs. 3%
Pazopanib **VEG 105129** **Sternberg et al 2013** **Sternberg et al 2010**	NF	• Advanced or metastatic RCC with clear cell component, previously treated • NCCN: Category 2A	• Oral • ECOG PS 0-1 • Pazopanib (N=290) vs. placebo (N=145) • Median follow-up: not reported, up to 24 mo • OS: 23 mo vs. 19 mo (not statistically significant) • PFS: 7.4 mo vs. 4.2 mo • ORR: 29% vs. 3%
Sunitinib **Motzer et al 2006**	NF	• Advanced or metastatic RCC with clear cell component, previously treated • NCCN: Category 2A	• Oral • ECOG PS 0-1 • Sunitinib (N=106) • Median follow-up: not reported • OS: 79% at 6 mo (median OS not reached) • PFS: 8.3 mo • ORR: 34%

Projected Place in Therapy

- Renal cell carcinoma (RCC) is a type of kidney cancer that accounts for 85% of kidney cancers, with a median age at diagnosis of 64 years. Approximately 70% of these have a clear cell histology or clear cell component.
- Tyrosine kinase inhibitors (TKIs) inhibiting vascular endothelial growth factor receptors (VEGFR), mammalian target of rapamycin (mTOR) inhibitors, and immune checkpoint inhibitors are common systemic therapy agents used in the first- and subsequent-line settings for treatment of advanced or metastatic RCC.
- Tivozanib is a TKI that is more selective for inhibition of VEGFR compared to its counterparts such as sorafenib, cabozantinib, lenvatinib, and several others. When compared to sorafenib, the TIVO-3 trial demonstrated a statistically significant progression-free survival (PFS) benefit. Reasonable toxicity, as 48% on tivozanib vs. 63% on sorafenib experienced adverse events leading to dose interruption and 24% vs. 38% experienced adverse events leading to dose reduction. According to the subgroup analyses, tivozanib may provide the most PFS benefit in patients with favorable- or intermediate- risk disease. However, tivozanib did not show a statistically significant OS benefit in the 3rd or 4th-line setting. This pattern of PFS benefit without an OS benefit is similar to the results of tivozanib versus sorafenib in the first-line setting.
- In the VA, tivozanib should be reserved for patients with advanced or metastatic RCC with clear-cell component, relapsed to 2 or 3 prior regimens including at least one prior VEGFR inhibitor, who are ineligible for or unable to tolerate other preferred systemic therapy options (lenvatinib/everolimus, cabozantinib, nivolumab).
- Choice of 3rd or 4th line therapy may be based on patient-specific factors (comorbidities, toxicity profile, once a day versus twice a day dosing, every day versus 21 out of 28 days, drug-drug interaction potential).

References

1. Kidney Cancer. National Comprehensive Cancer Network Guidelines. Version 4.2022. kidney.pdf (nccn.org)
2. Fotvida (tivozanib) [prescribing Information]. Boston, MA: AVEO Pharmaceuticals Inc; March 2021.
3. Rini B, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicenter, randomized, controlled, open-label study. *Lancet Oncol* 2020;21(1):95-104.
4. Pal SK, Escudier BJ, Atkins MB, et al. Final overall survival results from a phase 3 study to compare tivozanib to sorafenib as third- or fourth-line therapy in subjects with metastatic renal cell carcinoma. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.08.007
5. 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 of Clin Oncol* 31:3791-3799.
6. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomized, phase 2, open-label, multicenter trial. *Lancet Oncol* 2015;16:1473-1482.
7. Motzer RJ, Hutson TE, Ren M, et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. *Lancet Oncol* 2016;17:e4-5.
8. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015;373:1803-1813.
9. Motzer RJ, Escudier B, Powles T, et al. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma. *Br J Cancer* 2018;118:1176-1178.
10. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomized, open-label, phase 3 trial. *Lancet Oncol* 2016;17:917-927.
11. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1814-1823.
12. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-1068.
13. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomized, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49:1287-1296.
14. Hwang JP, Feld JJ, Hammond SP, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. *J Clin Oncol* 2020;38(31):3698-3715.

Prepared 04/2022. Contact person: Mark Geraci, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (10P4

Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information