

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212904Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

---

<b>Application Type</b>	NDA
<b>Application Number</b>	212904
<b>PDUFA Goal Date</b>	March 31, 2021
<b>OSE RCM #</b>	2020-661; 2020-663
<b>Reviewer Name(s)</b>	Till Olickal, Ph.D., Pharm.D.
<b>Team Leader</b>	Naomi Boston, Pharm.D.
<b>Deputy Director (Acting)</b>	Doris Auth, Pharm.D.
<b>Review Completion Date</b>	December 18, 2020
<b>Subject</b>	Review to determine if a REMS is necessary
<b>Established Name</b>	tivozanib
<b>Trade Name</b>	Fotivda
<b>Name of Applicant</b>	Aveo Pharmaceuticals Inc.
<b>Therapeutic Class</b>	Tyrosine kinase inhibitor
<b>Formulation(s)</b>	1.34 mg and 0.89 mg capsules
<b>Dosing Regimen</b>	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

## Table of Contents

EXECUTIVE SUMMARY .....	3
1 Introduction.....	3
2 Background .....	4
2.1 Product Information .....	4
2.2 Regulatory History.....	4
3 Therapeutic Context and Treatment Options .....	4
3.1 Description of the Medical Condition .....	4
3.2 Description of Current Treatment Options .....	5
4 Benefit Assessment.....	5
5 Risk Assessment & Safe-Use Conditions .....	7
6 Expected Postmarket Use.....	9
7 Risk Management Activities Proposed by the Applicant .....	10
8 Discussion of Need for a REMS .....	10
9 Conclusion & Recommendations .....	10
10 References .....	11

## EXECUTIVE SUMMARY

---

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Fotivda (tivozanib) is necessary to ensure the benefits outweigh its risks. Aveo Pharmaceuticals Inc. submitted a New Drug Application (NDA) 212904 for tivozanib with the proposed indication for the treatment of patients with relapsed or refractory renal cell carcinoma (RCC). The serious risks associated with the use of tivozanib are hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, impaired wound healing, reversible posterior leukoencephalopathy syndrome (RPLS), embryo-fetal toxicity and allergic reaction to tartazine. The applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

The Division of Risk Management (DRM) and the Division of Oncology Disease 1 (DO1) have determined that if approved, a REMS is not necessary to ensure the benefits of tivozanib outweigh its risks. RCC, also called renal adenocarcinoma (also called kidney cancer) is among the 10 most common cancers in both men and women. Despite overall improvements in outcomes of RCC due to targeted therapy against vascular endothelial growth factor (VEGF), these are not curative. There is a clear need for therapeutic strategies that encompass a better tolerated treatment option for RCC to be used as a single agent and in combinations. Tivozanib appeared efficacious in both its primary outcome of progression-free survival (PFS) and secondary outcomes of overall survival (OS) and objective response rate (ORR), and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of tivozanib for the treatment of adult patients with relapsed or refractory advanced RCC following two or more prior systemic therapies. The most concerning adverse reactions observed with the use of tivozanib are hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, impaired wound healing, RPLS, embryo-fetal toxicity and allergic reaction to tartazine. If tivozanib is approved, labeling, including information in Warnings and Precautions, Patient Counseling Information, and in the PPI will be used to communicate the safety issues and management of toxicities associated with tivozanib.

## 1 Introduction

---

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) tivozanib is necessary to ensure the benefits outweigh its risks. Aveo Pharmaceuticals Inc. submitted a New Drug Application (NDA) 212904 for tivozanib with the proposed indication for the treatment of patients with relapsed or refractory renal cell carcinoma (RCC).<sup>1</sup> The applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

## 2 Background

---

### 2.1 PRODUCT INFORMATION

Tivozanib is a NME NDA type 505(b)(1) pathway application.<sup>a</sup> It 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 including c-kit and PDGFR  $\beta$  at clinically relevant concentrations. In tumor xenograft models in mice and rats, tivozanib inhibited angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human renal cell carcinoma.<sup>1</sup> Tivozanib is available as in capsule strengths of 1.34 mg and 0.89 mg. The recommended dose of tivozanib is 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle) and for patients with moderate hepatic impairment, a reduced dose of 0.89 mg for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity.<sup>b</sup> Tivozanib was approved by European Medicines Agency (EMA) on August 24, 2017 for the first line treatment of adult patients with advanced RCC and for adult patients who are VEGFR and mammalian target of rapamycin (mTOR) pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for tivozanib (NDA 212904) relevant to this review:

- 05/30/2007: Investigation New Drug (IND) 075547 submission for tivozanib (AV-951; KRN951) was received.
- 05/31/2020: NDA 212904 submission for tivozanib with the proposed indication for the treatment of patients with relapsed or refractory RCC, received.
- 07/31/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tivozanib.

## 3 Therapeutic Context and Treatment Options

---

### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

RCC, also called renal adenocarcinoma (also called kidney cancer) is a disease in which malignant cells are found in the lining of tubules in the kidney. Approximately 85% of renal cell cancers are adenocarcinomas, and most of those are of proximal tubular origin. Most of the remainder are transitional cell carcinomas of the renal pelvis.<sup>2</sup> Kidney cancer is among the 10 most common cancers in both men and women. The lifetime risk for developing kidney cancer is about 1 in 46 (2.02%) and 1 in 82 (1.02%) in men and women, respectively.<sup>3</sup> There is a 1.5:1 predominance in men over women, with peak incidence occurring between 60 and 70 yr of age. Etiological factors include lifestyle variables such as smoking, obesity, and hypertension.<sup>4</sup> The expected number of new cases of RCC in the United States in

---

<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>b</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2020 is 73,750<sup>c</sup>, with 14,830 expected deaths due to the disease.<sup>d,2,5</sup> The American Cancer Society estimates approximately 45,520 men and 28,230 women will be diagnosed with kidney cancer in the United States in 2020, and approximately 9,860 men and 4,970 women will die in 2020 as a result of this cancer.<sup>3</sup> Five-year survival for patients diagnosed with kidney cancer is approximately 75.2%. Approximately 1.7 percent of men and women will be diagnosed with kidney and renal pelvis cancer at some point during their lifetime, based on 2015–2017 data.<sup>5,d</sup>

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The mainstay of treatment of the RCC is Surgical resection.<sup>2</sup> Over the past 12 years, medical treatment for RCC has transitioned from a nonspecific immune approach (in the cytokine era), to targeted therapy against VEGF, and now to novel immunotherapy agents.<sup>6</sup> In newly diagnosed RCC, a quarter of patients will present with metastatic RCC (mRCC), while an additional 20–40% who initially present with localized disease will go on to develop mRCC. Metastatic RCC portends a poor prognosis with median overall survival (OS) less than three years. In the 1990s, treatment of mRCC was limited to high dose interleukin-2<sup>7</sup> and interferon-alfa.<sup>8</sup> Both treatments had poor response rates and significant toxicities. Then, improved understanding of the molecular pathways involved in the pathogenesis of mRCC led to the development of novel first-line treatments, including VEGF tyrosine kinase inhibitors (TKIs), such as sorafenib<sup>9</sup>, sunitinib<sup>10</sup>, pazopanib<sup>11</sup>, a monoclonal antibody against VEGF (bevacizumab<sup>12</sup>), and mTOR inhibitors (temsirolimus<sup>13</sup>). These agents improved survival outcomes for patients with mRCC. In the past few years, multi-target TKIs and immune checkpoint inhibitors have again changed first-line treatment for mRCC. Among multi-target TKIs, cabozantinib<sup>14</sup>, a VEGF, MET, and AXL TKI, was approved for first-line treatment of mRCC. Combination therapies, including immune checkpoint inhibitors and VEGF targeted therapy, were the next evolution in first-line treatment.<sup>8</sup> The treatment landscape for RCC is changing with the introduction of next-generation VEGF-targeted therapies, immunotherapy agents including checkpoint inhibitors (programmed cell death-1 protein (PD-1) inhibitor, nivolumab<sup>15</sup> and cytotoxic T-lymphocyte-associated protein 4 inhibitors (CTLA4) such as ipilimumab<sup>16</sup> and pembrolizumab<sup>17</sup>) and combination regimens.<sup>6</sup> The combination immunotherapy has resulted in significantly higher rates of immune-related adverse events compared to PD-1 inhibitor monotherapy. Although VEGFR TKIs have improved efficacy, they are often associated with tolerability issues that frequently require dose reductions and interruptions. There is a clear need for therapeutic strategies that encompass a better tolerated treatment option for RCC to be used as a single agent and in combinations.

## 4 Benefit Assessment

---

The efficacy of tivozanib was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open-label, multicenter trials 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. Patients were randomized to receive tivozanib 1.34 mg orally once daily for 21 days on

---

<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

<sup>d</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

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.<sup>1</sup>

The following section is a summary of relevant efficacy information to date for tivozanib. Randomization was stratified by prior therapy [two kinase inhibitors (KIs), a KI plus an immune checkpoint inhibitor, or a KI plus other systemic agents] and by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score. The main 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). A statistically significant improvement in PFS was observed in the tivozanib arm compared to the sorafenib arm with a hazard ratio of 0.73 (95% CI: 0.56, 0.94) is shown in Table 1.<sup>1,18,19,e</sup> The estimate of median PFS was 5.6 months for the tivozanib arm and 3.9 months for the sorafenib arm.

The key secondary supportive efficacy end points are overall survival (OS) and objective response rate (ORR). The final analysis was performed based on a data cutoff date of May 1<sup>st</sup>, 2020. As of that cutoff date, 251 death events have occurred. The results of the OS final analysis are summarized in Table 1.<sup>1,18,19</sup> The median OS favored sorafenib by about 3 months (16 months in tivozanib vs. 19 months in sorafenib). The objective response rate included confirmed complete response rate and confirmed partial response based on RECIST v1.1 and was calculated in the intent-to-treatment population. As shown in Table 1, the tivozanib arm had an ORR rate per BIRR of 18% and the sorafenib arm had a rate of 8%.

**Table 1: Efficacy Results in TIVO-3 (ITT)<sup>1,18,19,e</sup>**

Endpoint	Tivozanib N= 175	Sorafenib N= 175
<b>Progression Free Survival (PFS)*</b>		
Events, n (%)	123 (70)	123 (70)
Progressive Disease	103 (59)	109 (62)
Death	20 (11)	14 (8)
Median (95% CI), months	5.6 (5.3, 7.3)	3.9 (3.7, 5.6)
HR (95% CI) †	0.73 (0.56, 0.95)	
P-value <sup>††</sup>	0.016	
<b>Overall Survival</b>		
Deaths, n (%)	125 (71)	126 (72)
Median (95% CI), months	16.4 (13.4, 21.9)	19.2 (14.9, 24.2)
HR (95% CI) †	0.97 (0.75, 1.24)	
<b>Objective Response Rate % (95% CI)*</b>	18 (12, 24)	8 (4, 13)
Median duration of response in months (95% CI)	NE (9.8, NE)	5.7 (5.6, NE)
CI: Confidence interval; HR: Hazard ratio (FOTIVDA/sorafenib); NE: not estimable *Assessed by blinded independent radiology review committee according to RECIST v1.1. †Based on the Cox proportional hazards model stratified by IMDC prognostic score and prior therapy. ††Based on the log-rank test stratified by IMDC prognostic score and prior therapy.		

<sup>e</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

## 5 Risk Assessment & Safe-Use Conditions

---

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for tivozanib. The safety of tivozanib was evaluated in TIVO-3, a randomized, open-label trial patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments. A total of 350 patients were randomized (1:1) to receive tivozanib 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. Among patients who received tivozanib, 53% were exposed for 6 months or longer and 31% were exposed for greater than one year.<sup>1</sup>

The most common ( $\geq 20\%$ ) adverse reactions reported in the tivozanib treatment arm compared with sorafenib treatment arm were fatigue (67% versus 48%), hypertension (44% versus 31%), diarrhea (43% versus 54%), decreased appetite (39% versus 30%), nausea (30% versus 18%), dysphonia (27% versus 9%), hypothyroidism (24% versus 11%), cough (22% versus 15%), and stomatitis (21% versus 23%), and the most common grade 3 or 4 laboratory abnormalities ( $\geq 5\%$ ) were sodium decreased (9% versus 11%), lipase increased (9% versus 10%), and phosphate decreased (5% versus 31%).<sup>1</sup>

### Deaths

A total of 9.2% (n=16/175) deaths was reported in the tivozanib group compared with 8.2% (n=14/175) in the sorafenib group. Of the 16 deaths reported, 4 deaths were due to neoplasm progression and 12 were from AEs. Of the 12 deaths from AEs, at least half occurred in the context of disease progression. The other 6 included 2 deaths where the patient was already deteriorating at enrollment, 1 which resulted in pneumonia, and the other was pneumonia leading to respiratory failure. For the remaining 4 grade 5 AEs, one which resulted in pneumonia, the second patient had pneumonia secondary to CVA in a patient with history of radiation therapy to brain for metastases and intrabronchial radiation therapy to lung, one patient had respiratory failure secondary to smoking and the fourth patient had as sudden death who had been hospitalized for grade 3 chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) exacerbation 1 month prior.<sup>1818</sup>

### Serious Adverse Events (SAE)

Serious adverse reactions occurred in 45% of patients who received tivozanib. Serious adverse reactions in  $> 2\%$  of patients included bleeding (3.5%), venous thromboembolism (3.5%), arterial thromboembolism (2.9%), and hepatobiliary disorders (2.3%). Permanent discontinuation of tivozanib due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent discontinuation of tivozanib in  $> 2\%$  of patients included hepatobiliary disorders and fatigue. Dosage interruptions of tivozanib due to an adverse reaction occurred in 48% of patients. Adverse reactions which required dosage interruption in  $> 5\%$  of patients included fatigue, hypertension, decreased appetite, and nausea. Dose reductions of tivozanib due to an adverse reaction occurred in 24% of patients. Adverse reactions which required dose reductions in  $> 3\%$  of patients included fatigue, diarrhea, and decreased appetite.<sup>1</sup>

If approved, labeling will include the following risks in the Warnings and Precautions section, which will reflect the pooled safety population in 1008 patients with advanced RCC in TIVO-3 and five other



monotherapy studies at a dose of tivozanib administered at 1.34 mg orally once daily with or without food for 21 days on treatment followed by 7 days off treatment for a 28-day cycle. Among the 1008 patients who received tivozanib included, 52% were exposed for 6 months or longer and 34% were exposed for greater than one year.<sup>1</sup>

### **5.1 HYPERTENSION AND HYPERTENSIVE CRISIS**

In the pooled safety population, hypertension occurred in 45% (n=454/1008) of patients treated with tivozanib, with 22% (n=223/1008) of the events  $\geq$  Grade 3; the median time to onset of hypertension was 2 weeks (range: 0 – 192 weeks). Hypertensive crisis occurred in 0.8% of patients. One patient (0.1%) died due to hypertensive emergency after tivozanib overdose. Blood pressure should be controlled prior to treatment with tivozanib; blood pressure monitoring dose adjustment recommendations are provided in the dose adjustment algorithm found in both Warnings and Precautions and the Dosage and Administration sections of the label.<sup>1</sup>

### **5.2 CARDIAC FAILURE**

Cardiac failure occurred in 1.6% of the tivozanib-treated pooled safety population with 1% of events  $\geq$  Grade 3; 0.6% of events were fatal. Periodic monitoring for symptoms of cardiac failure throughout treatment with tivozanib and recommendations to adjust or hold dosing as needed, according to the dose adjustment algorithm to address the safety issues with tivozanib will also be included in both Warnings and Precautions and the Dosage and Administration sections of the label.<sup>1</sup>

### **5.3 CARDIAC ISCHEMIA AND ARTERIAL THROMBOEMBOLIC EVENTS**

Treatment with tivozanib can cause serious, sometimes fatal, cardiac ischemia and arterial thromboembolic events. Cardiac ischemia in tivozanib-treated patients occurred in 3.1%, with 1.4% of events  $\geq$  Grade 3, and 0.3% of events were fatal. Arterial thromboembolic events were reported in 2% of tivozanib-treated patients, including death due to ischemic stroke (0.1%). Patients who are at risk for, or who have a history of these events (such as myocardial infarction and stroke) should be closely monitored, during treatment with tivozanib and tivozanib should be discontinued in patients who develop any grade of arterial thromboembolic event. These events will be included in both Warnings and Precautions and the Dosage and Administration sections of the label.<sup>1</sup>

### **5.4 VENOUS THROMBOEMBOLIC EVENTS**

Venous thromboembolic events occurred in 2.4% (n=24/1008) of patients treated with tivozanib, including death (0.3%). Labeling instructs to closely monitor patients who are at risk for or who have a history of these events during treatment with tivozanib and to discontinue tivozanib in patients who develop severe or life-threatening venous thromboembolic events.<sup>1</sup>

### **5.5 HEMORRHAGIC EVENTS**

Hemorrhagic events occurred in 11% (n=113/1008) of patients treated with tivozanib, including death (0.2%). Labeling instructs to closely monitor patients who are at risk for or who have a history of bleeding during treatment with tivozanib and to discontinue tivozanib in patients who develop grade 3 or 4, which be included in both Warnings and Precautions and the Dosage and Administration sections of the label.<sup>1</sup>

## 5.6 PROTEINURIA

Proteinuria occurred in 8% (n=81/1008) of tivozanib-treated patients with 2% (n=19/1008) of events Grade 3. Of the patients who developed proteinuria, 3/81 (3.7%) had acute kidney injury either concurrently or later during treatment. Patients should be monitored for proteinuria before initiation of, and periodically throughout, treatment with tivozanib should be discontinued in patients who develop nephrotic syndrome. Recommendations to adjust or hold dosing as needed, according to the dose adjustment algorithm to address the safety issues with tivozanib will also be included in both Warnings and Precautions and the Dosage and Administration sections of the label.<sup>1</sup>

## 5.7 THYROID DYSFUNCTION

Thyroid dysfunction events in tivozanib-treated patients occurred in 8%, with 0.2% Grade 3 or 4 events. Hypothyroidism was reported in 8% of patients and hyperthyroidism was reported in 1% of patients. Labeling instructs to monitor thyroid function before initiation of, and periodically throughout, treatment with tivozanib.

## 5.8 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, tivozanib can cause fetal harm when administered to a pregnant woman. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential during treatment with tivozanib and for one month after the last dose will be communicated in the Use in Specific Populations section of the label.<sup>1</sup>

## 5.9 ALLERGIC REACTIONS TO TARTRAZINE (FD&C YELLOW No.5)

Tivozanib 0.89 mg capsule contains FD&C Yellow No.5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients. Labeling communicates that 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 hypersensitivity.

Other adverse events that tivozanib has in common with currently approved kinase inhibitors<sup>9,10,11,14</sup>, will likely be communicated in the Warnings and Precautions section of the tivozanib as well. These adverse events include: risk of impaired wound healing and reversible posterior leukoencephalopathy syndrome (RPLS).<sup>1</sup>

## 6 Expected Postmarket Use

---

According to the current proposed indication, if approved, tivozanib will be used in both inpatient and outpatient settings. It is expected that oncologists, familiar with the management of toxicities such as hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, impaired wound healing, RPLS, embryo-fetal toxicity and allergic reaction to tartrazine, will be the likely prescribers of tivozanib.

## 7 Risk Management Activities Proposed by the Applicant

---

The applicant did not propose any risk management activities for tivozanib beyond routine pharmacovigilance and labeling. The applicant proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, and a PPI to address the risks of hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, impaired wound healing, RPLS, embryo-fetal toxicity and allergic reaction to tartazine.

## 8 Discussion of Need for a REMS

---

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for tivozanib, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Tivozanib is a tyrosine kinase inhibitor, with the proposed indication for the treatment of patients with relapsed or refractory RCC. Based on the efficacy and safety information currently available, the clinical reviewers stated that tivozanib shows clinically meaningful benefit, and recommend approval of tivozanib for the treatment of adult patients with relapsed or refractory advanced RCC following two or more prior systemic therapies.<sup>1,18,19</sup>

RCC is among the 10 most common cancers in both men and women. Despite overall improvements in outcomes of RCC due to targeted therapy against VEGF, they are not curative. There is a clear need for therapeutic strategies that encompass a better tolerated treatment option for RCC to be used as a single agent and in combinations. Tivozanib appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.<sup>1,18,19</sup> The likely prescribers for tivozanib will be oncologists. The risks identified are risks that these providers have likely encountered in their practice experience and can manage without additional risk mitigation measures.

DRM and DO1 have determined that if approved, a REMS is not necessary to ensure the benefits of tivozanib outweigh its risks. The most concerning adverse reactions observed with the use of tivozanib are of hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, impaired wound healing, RPLS, embryo-fetal toxicity and allergic reaction to tartazine. At the time this review was completed, labeling negotiations were still ongoing with the Applicant; if tivozanib is approved, Warnings and Precautions in the labeling, will be used to communicate the safety issues and management of toxicities associated with tivozanib, as well as information to be included in Patient Counseling Information and a PPI to inform patients.

## 9 Conclusion & Recommendations

---

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of tivozanib. The management of the risks associated with tivozanib treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

## 10 References

---

- <sup>1</sup> Draft Prescribing Information for tivozanib as currently edited by the FDA, last updated December 7, 2020.
- <sup>2</sup> National Institutes of Health (NIH). National Cancer Institute (NCI). Renal Cell Cancer Treatment. [https://www.cancer.gov/types/kidney/hp/kidney-treatment-pdq#\\_228\\_toc](https://www.cancer.gov/types/kidney/hp/kidney-treatment-pdq#_228_toc). Accessed December 9, 2020.
- <sup>3</sup> American Cancer Society. Key Statistics About Kidney cancer. <https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html>. Accessed December 9, 2020.
- <sup>4</sup> Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*. 2015;67(5):913-924.
- <sup>5</sup> National Institutes of Health (NIH). The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). Cancer Stat Facts: Kidney and Renal Pelvis Cancer. <https://seer.cancer.gov/statfacts/html/kidrp.html>. Accessed December 9, 2020.
- <sup>6</sup> Barata PC, Rini BI. Treatment of renal cell carcinoma: Current status and future directions. *CA Cancer J Clin*. 2017;67(6):507-524.
- <sup>7</sup> Proleukin. Prescribing Information (last updated 07/2012)
- <sup>8</sup> Hahn AW, Hale P, Maughan BL, Haaland B, Agarwal N. Optimal First-Line Treatment of Metastatic Renal-Cell Carcinoma: A Network Meta-Analysis. *Kidney Cancer*. 2018;2:115-121.
- <sup>9</sup> Nexavar. Prescribing Information (last updated 06/2020).
- <sup>10</sup> Sutent. Prescribing Information (last updated 08/2020).
- <sup>11</sup> Votrient. Prescribing Information (last updated 08/2020).
- <sup>12</sup> Avastin. Prescribing Information (last updated 12/2020).
- <sup>13</sup> Torisel. Prescribing Information (last updated 03/2018).
- <sup>14</sup> Cabometyx. Prescribing Information (last updated 07/2020).
- <sup>15</sup> Opdivo. Prescribing Information (last updated 11/2020)
- <sup>16</sup> Yervoy. Prescribing Information (last updated 11/2020).
- <sup>17</sup> Keytruda. Prescribing Information (last updated 11/2020)
- <sup>18</sup> Chang E and Zhang L. Clinical-Statistical Review Presentation. Mid-Cycle Meeting, dated July 16, 2020.
- <sup>19</sup> DO1 Multi-disciplinary Review and Evaluation (draft) for NDA 212904 tivozanib, dated December 10, 2020.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

TILL OLICKAL  
12/18/2020 04:27:27 PM

NAOMI S BOSTON  
12/18/2020 07:47:24 PM

DORIS A AUTH  
12/18/2020 08:24:03 PM