Tivozanib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Tivozanib for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC	C64	00564a	CDS - 01/10/2019

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Tivozanib is taken once daily for 21 days followed by a seven day rest period. Each treatment cycle is 28 days. Treatment is continued until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-21	Tivozanib	1340 microgram	PO		28 days
Tivozanib may be taken with or without food. The capsules must be swallowed whole with a glass of water and must not be opened.					
In the case of a missed dose or if vomiting occurs, a replacement dose should not be taken. The next dose should be taken at the next scheduled time.					

ELIGIBILITY:

- Indications as above
- Histologically confirmed RCC with a clear cell component by an approved and validated test method
- 0-1 prior therapies for metastatic RCC
- ECOG performance status of 0-1
- Adequate organ and haematological function

EXCLUSIONS:

- Hypersensitivity to tivozanib or any of the excipients
- Prior VEGF-targeted therapy or mTOR pathway targeted therapy
- Pregnant or lactating females.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

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TESTS:

Baseline tests:

- Baseline confirmation that the patient's RCC tumour has a clear cell component by an accurate and validated test method
- FBC, renal and liver profile
- ECG
- Electrolyte monitoring (calcium, magnesium, potassium)
- TFTs
- Blood pressure
- Dipstick urinalysis for protein

Regular tests:

- FBC, renal and liver profile
- TFTs
- Blood pressure
- Dipstick urinalysis for protein

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- The occurrence of undesirable effects may require temporary interruption and/or dose reduction of tivozanib therapy.
- In the pivotal study, the dose was reduced for grade 3 events and interrupted for grade 4 events.
- When dose reduction is necessary, the tivozanib dose can be reduced to 890 microgram once daily with the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period (Table 1).

Table 1: Tivozanib recommended dose reduction levels

Dose level	Tivozanib
Recommended starting dose*	1340 microgram
One dose level reduction	890 microgram
*Recommended starting dose in moderate hepatic impairment is 1340 microgram on alternative days	

Haematological:

Table 2: Recommended dose modification of tivozanib in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1.0	And	≥50	100% dose
0.5-1.0	or	25-50	Reduce dose by one dose reduction
<0.5	or	<25	interrupt dose until recovery to Grade ≥2 Reduce dose by one dose reduction

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Renal and Hepatic Impairment:

Table 3: Recommended dose modification of tivozanib in renal and hepatic impairment

Severity	Renal Impairment	Hepatic Impairment
Mild	No dose adjustment is required	Use with caution. Close monitoring of tolerability advised / monitor for adverse events
Moderate	No dose adjustment is required	Reduce starting dose to 1340 microgram on alternate days. Use with caution. Close monitoring of tolerability advised / monitor for adverse events
Severe	Caution advised due to limited experience. No data available for patients undergoing dialysis	Not recommended

Management of adverse events:

Table 4: Recommended dose modification of tivozanib for Adverse Events

Adverse reactions	Severity*	Dose modification
Proteinuria	Grade 2 or Grade 3	Reduce dose or interrupt treatment
	Grade 4	Permanent discontinuation of treatment
Other	Grade 1 and 2	Continue treatment at the same dose
	Grade 3 • First occurrence • Second occurrence	Reduce dose Interrupt treatment until the adverse reaction resolves. Add supportive care as indicated. Re-initiate at a reduced dose
	Grade 4	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤2, re-initiate at a reduced dose.

* National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Tivozanib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Hypertension:** Cases of hypertension have been reported in clinical studies with tivozanib. Blood pressure should be well controlled prior to initiating tivozanib. In the case of persistent hypertension despite use of anti-hypertensive therapy, the tivozanib dose should be reduced, or the treatment interrupted and re-initiated at a lower dose once the blood pressure is controlled, according to clinical judgment. Discontinuation of treatment should be considered in cases of persistent severe hypertension, posterior reversible encephalopathy syndrome, or other

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complications of hypertension. Patients receiving anti-hypertensive medication should still be monitored for hypotension when tivozanib is either interrupted or discontinued.

- **Arterial/venous thromboembolic events**: Cases of arterial thromboembolic events (ATEs) and venous thromboembolic events (VTEs) have occurred in clinical studies with tivozanib. Tivozanib has not been studied in patients who had an ATE or VTE within the preceding 6 months of clinical study initiation. Tivozanib must be used with caution in patients who are at risk of or who have a history of ATE/VTE
- **Cardiac failure**: Cases of cardiac failure have been reported in clinical studies with tivozanib. Signs or symptoms of cardiac failure should be periodically monitored throughout treatment with tivozanib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of tivozanib therapy, plus treatment of potential underlying causes of cardiac failure e.g. hypertension.
- **Haemorrhage:** In clinical studies with tivozanib, haemorrhagic events have been reported. Tivozanib must be used with caution in patients who are at risk for, or who have a history of bleeding. If any bleeding requires medical intervention, tivozanib should be temporarily interrupted.
- **Proteinuria**: Proteinuria has been reported in clinical studies with tivozanib. Monitoring for proteinuria before initiation of, and periodically throughout treatment is recommended. For patients who develop Grade 2 (> 1.0-3.4 g/24 hours) or Grade 3 (≥ 3.5 g/24 hours) proteinuria, the dose of tivozanib has to be reduced or the treatment temporarily interrupted. If the patient develops Grade 4 proteinuria (nephrotic syndrome) tivozanib has to be discontinued.
- **Hepatotoxicity:** In clinical studies with tivozanib, elevations of ALT, AST and bilirubin have been reported. The majority of AST and ALT elevations were not accompanied with concomitant elevations of bilirubin. AST, ALT, bilirubin, and AP should be monitored before initiation of and periodically throughout treatment with tivozanib because of the potential risk of hepatotoxicity.
- **Hand foot skin reaction**: In clinical studies with tivozanib, hand foot skin reaction (palmar-plantar erythrodysaesthesia) has been reported. Management of patients experiencing HFSR may include topical therapies for symptomatic relief with consideration of temporary interruption and/or reduction in treatment dose or, in severe or persistent cases, permanent discontinuation of treatment.
- **QT interval prolongation**: In clinical studies with tivozanib, QT/QTc interval prolongation has been reported. It is recommended that tivozanib be used with caution in patients with a history of QT interval prolongation or other relevant pre-existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended.
- **Gastrointestinal perforation/fistula**: It is recommended that symptoms of gastrointestinal perforation or fistula should be periodically monitored throughout treatment with tivozanib and that tivozanib should be used with caution in patients at risk for GI perforation or fistula.
- **Wound healing complications**: For precautionary reasons, temporary interruption of tivozanib therapy is recommended in patients undergoing major surgical procedures. The decision to resume tivozanib therapy after surgery should be based on clinical judgment of adequate wound healing.
- **Hypothyroidism:** In clinical studies with tivozanib, hypothyroidism has been reported. Hypothyroidism has been observed to occur at any time during treatment with tivozanib, developing as early as within two months of treatment initiation. Thyroid function should be monitored before initiation of, and periodically throughout treatment with tivozanib. Hypothyroidism should be treated according to standard medical practice.

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- **Tartrazine:** Tivozanib 890 microgram hard capsules contain tartrazine (E102) which may cause allergic reactions.
- **Women of childbearing potential/contraception in males and females:** Women of childbearing potential should avoid becoming pregnant while on tivozanib. Female partners of male patients taking tivozanib should also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least one month after completing therapy. It is currently unknown whether tivozanib may reduce the effectiveness of hormonal contraceptives and therefore women using hormonal contraceptives should add a barrier method.
- **Aneurysms and artery dissections:** The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating tivozanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.
- **Elderly patients:** Dysphonia, diarrhoea, fatigue, weight decreased, appetite decreased and hypothyroidism occurred more commonly in patients ≥ 65 years of age. Healthcare professions should be aware that elderly patients may be at increased risk of adverse reactions.

DRUG INTERACTIONS:

- Caution with administration of tivozanib with strong CYP3A4 inducers. Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure.
- Herbal preparations containing St. John's wort (*Hypericum perforatum*) are contraindicated.
- Caution with BCRP substrates which have a clinically-relevant efflux interaction in the gut
    - ensure that a suitable time window (e.g. 2 hours) is applied between administration of tivozanib and the BCRP substrate
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Motzer RJ 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 Oct 20;31(30):3791-9
2. Tivozanib (Fotivda®) Summary of Product Characteristics. Accessed Sept 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/fotivda-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	24/07/2019		Prof Maccon Keane
2	23/06/2021	Reviewed. Updated adverse events section.	Prof Maccon Keane
3	23/09/2021	Amendment made to dosage form to correctly include as microgram in Treatment table, Table 1 and Table 3.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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