# Tivozanib

## Indication
First line treatment of patients with advanced and/or metastatic renal cell carcinoma

## Regimen details
Tivozanib 1340 micrograms orally daily for 21 days

## Cycle frequency
Every 4 weeks (i.e. “Three weeks on, one week off”)

## Number of cycles
Until disease progression

## Administration
If a dose is missed or the patient vomits after taking their dose, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

## Pre-medication
None

## Emetogenicity
No routine antiemetics required

## Additional supportive medication
Nil

## Extravasation
N/A

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| LFT (including AST) | 14 days |
| TFTs | 14 days |
| Blood pressure | 14 days |
| Urinalysis for proteinuria | 14 days |
| ECG | 14 days |

Blood pressure must be well controlled before initiating treatment with tivozanib

The use of vascular endothelial growth factor (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

Temporary interruption of tivozanib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major

surgical intervention. Therefore, the decision to resume tivozanib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery

Tivozanib should be used with caution in patients with a history of QT prolongation, or other relevant pre-existing cardiac disease, and those receiving other medications known to increase the QT interval

## Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), blood pressure
TFTs every 12 weeks
ECG if clinically indicated
Periodic urinalysis for proteinuria

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

| **Investigation** | **Limit** |
|---|---|
| Neutrophil count | ≥ 1.0 x $10^9$/L |
| Platelet count | ≥ 100 x $10^9$/L |
| Creatinine clearance | ≥ 30 mL/min |
| AST/ALT | < ULN |
| Bilirubin | < ULN |
| Blood pressure | < 140/90 mmHg |

## Dose modifications

Haematological toxicity
Discuss with clinician if neutrophils < 1.0 x $10^9$/L and/or platelets < 100 x $10^9$/L

Renal impairment
No dose modifications are required for mild-moderate renal impairment. Caution is advised in severe renal impairment or in patients undergoing dialysis as there is limited experience of use in such patients

Hepatic impairment
Tivozanib should be used with caution in patients with mild- moderate hepatic impairment and with close monitoring for toxicity. Patients with moderate hepatic impairment should be prescribed 1,340mcg on alternate days with close monitoring

Hypertension
Hypertension is common, especially within the first 2 months of treatment – patients should be closely monitored and treated as needed with anti-hypertensives.

If hypertension is persistent despite antihypertensive treatment, consider a dose interruption followed by a dose reduction.

Treatment should be discontinued if persistent severe hypertension, posterior reversible encephalopathy or other complications of hypertension

Palmar Plantar Erythema (Hand and Foot Syndrome)
If hands and/or feet become blistered, or if pain relief is required, consider a 1-2 week break in treatment until resolved to Grade ≤ 1. The patient should be advised to moisturise their hands and feet regularly, and to keep them cool. The patient may also be advised to take care to minimise excessive periods of pressure on their feet. On recovery consider dose reduction

Proteinuria
If grade 2 or grade 3 proteinuria, reduce the tivozanib dose, or interrupt treatment until resolved. If the patient develops grade 4 proteinuria (nephrotic syndrome), discontinue tivozanib

## Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Arterial thromboembolic events
Venous thromboembolic events
Cardiac failure
Haemorrhage
Hepatotoxicity
Nephrotic syndrome
Posterior reversible encephalopathy syndrome
QT prolongation
GI perforation
Hypothyroidism

- **Frequently occurring side effects**

Hypertension
Palmar plantar erythema
Dysphonia
Fatigue
Reduced appetite
Weight loss
Insomnia
Headache
Peripheral neuropathy
Dizziness
Cough, dyspnoea
Epistaxis
Nausea, diarrhoea, abdominal pain
Myalgia, arthralgia, back pain

- **Other side effects**

Visual disturbances
Tinnitus

## Significant drug interactions

– for full details consult product literature/ reference texts

Herbal preparations containing St. John's wort are contraindicated. If a patient is taking St John's wort, this should be stopped at least 2 weeks before starting tivozanib.

Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin or alternative oral anticoagulant.

Strong CYP3A4 inducers: (e.g. rifampicin) concomitant administration should be avoided or undertaken with caution (increased exposure of tivozanib)

Medicinal products for which intestinal absorption is restricted by BCRP: Tivozanib inhibits the transporter protein BCRP in vitro (but the clinical relevance of this finding is unknown). Caution should be exercised if tivozanib is co-administered with rosuvastatin. Patients taking an oral BCRP substrate with a clinically-relevant efflux interaction in the gut should ensure that a suitable time window (e.g. 2 hours) is allowed between administration of tivozanib and the BCRP substrate.

Medications causing QT prolongation: use with caution.
Contraceptives: It is currently unknown whether tivozanib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method

## Additional comments

## References

South West Clinical Network Cancer Protocols - http://www.swscn.org.uk/guidance-protocols/cancer-protocols/

Tivozanib SPC - https://www.medicines.org.uk/emc/product/8995/smpc

**THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, DESIGNATED LEAD CLINICIAN FOR KIDNEY CANCER**

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

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