Tivozanib

Indication
First line treatment of advanced renal cell carcinoma.

(NICE TA512)

ICD-10 codes
Codes with a prefix C64

Regimen details

Day	Drug	Dose	Route
1-21	Tivozanib	1,340 micrograms OD	PO

Cycle frequency
28 days (21 days of treatment followed by 7 days rest).

Number of cycles
Continued until disease progression or unacceptable toxicity.

Administration
Tivozanib is available as 890 micrograms (mcg) and 1,340mcg capsules. The capsules may be taken with or without food. They should be swallowed whole with a glass of water and should not be opened.

If a dose is missed or the patient vomits following the dose, a replacement dose should not be taken. The next dose should be taken at the next scheduled time.

Pre-medication
Nil

Emetogenicity
This regimen has moderate-low emetic potential.

Additional supportive medication
Antiemetics as per local policy
Loperamide if required.
Patients should be advised to use regular moisturiser for their hands and feet throughout treatment.

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Calcium and Magnesium	14 days
Blood pressure	Baseline
Thyroid function tests (TFTs)	Baseline
Urinalysis (to assess for proteinuria)	Baseline
ECG	Baseline

Blood pressure must be well controlled prior to commencing treatment.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U+Es (including creatinine)	Monthly
LFTs	Monthly
Calcium and magnesium	As clinically indicated
Blood pressure	Every 2 weeks for the first 2 months, then monthly or as clinically indicated.
TFTs	Every 12 weeks or as clinically indicated
Urinalysis (to assess for proteinuria)	As clinically indicated

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
CrCl	>30mL/min
ALT/AST	< 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.

Tivozanib is not recommended in patients with severe renal impairment.

- **Other toxicities**

Consider a dose reduction for any grade 3 toxicity. If a patient experiences grade 4 toxicity the dose should be withheld and only recommenced after recovery with a dose reduction.

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.

Surgery:
Tivozanib may delay would healing so should be stopped at least 7 days prior to surgery and only recommenced once any wounds are adequately healed.

Palmar-plantar erythema:
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.

QT prolongation:
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.

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

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 512 accessed 1 May 2019 via www.nice.org.uk
- Summary of Product Characteristics – Tivozanib (Eusa Pharma) accessed 1 May 2019 via www.medicines.org.uk
- Motzer, R et al; Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. JCO 2013; 31 (30): 3791 – 3799.

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