Indication	For metastatic or inoperable locally advanced renal cell carcinoma with a clear cell component. Note: papillary, chromophobe and Xp11 translocation sub types can be treated as per clear cell pathway. NB: patients must have either not previously received any VEGF-targeted therapy or mTOR pathway inhibitor-targeted therapy **unless** they have received 1st line treatment with avelumab and axitinib or had immediate prior treatment with either with pazopanib or sunitinib which has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression. Patients treated with tivozanib may switch to pazopanib or sunitinib where treatment has to be stopped early under the same circumstances.
Treatment Intent	Palliative treatment
Frequency and number of cycles	Every 28 days Continue until progressive disease or unacceptable toxicity or patient choice Review by the end of the first 8 weeks of treatment
Monitoring parameters pre-treatment	• Monitor FBC, LFT's (AST, ALT, bilirubin, and AP) and U&E's prior to each cycle. Calcium, magnesium and potassium should be maintained within the normal range. • **Hepatic impairment:** Not recommended in severe hepatic impairment. Patients with moderate hepatic impairment should be treated with 1340 microgram every other day. No dose adjustment is required in mild hepatic impairment. Tivozanib should be used with caution in patients with mild and moderate hepatic impairment with close monitoring of tolerability. • **Renal impairment:** No dose adjustment is required in patients with mild or moderate renal impairment. Caution in patients with severe (<30ml/min) renal impairment (limited data). • If neuts <1.0 and/or PLT <50 d/w consultant • Thyroid function should be monitored before initiation of treatment, and every 8 weeks throughout. • ECG prior to initiating treatment and then as clinically indicated. • ECHO at baseline for at risk patients and repeated every 6 months. • **Hypertension and proteinuria:** Monitor blood pressure (BP) every 2 weeks for the first 2 months and then before each cycle, BP should be well controlled. Proteinuria should be checked prior to starting treatment and before each cycle. Hypertension should be treated as needed with anti-hypertensive therapy. Patients receiving anti-hypertensive medication should be monitored for hypotension when tivozanib is either interrupted or discontinued. 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 BP is controlled. Dose reduce or interrupt treatment in patients who develop Grade 2 (> 1.0-3.4 g/24 hours) or Grade 3 (≥ 3.5 g/24 hours) proteinuria.

	• **Venous / arterial thromboembolic events:** Use with caution in patients at risk of, or who have a history of arterial thromboembolic events. Use of tivozanib in patients who are at risk of VTEs, should be based on individual patient benefit/risk assessment. • **Cardiac failure:** Signs or symptoms of cardiac failure should be periodically monitored throughout treatment. • **QT interval prolongation:** Use 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. • **Bleeding / wound healing:** Use with caution in patients who are at risk of, or who have a history of bleeding, GI perforation or fistula. 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. • **Posterior reversible encephalopathy syndrome (PRES):** The safety of re-initiating tivozanib in patients previously experiencing PRES is not known and tivozanib should only be used with caution in these patients. • **Hand Foot Skin Reaction:** Emollients should be initiated at first sign of hand foot skin reaction. Consider temporary interruption and/or reduction in treatment dose. • **Dose modifications / interruption of treatment***:* Reduce dose to 890 microgram once daily for 21 days followed by a 7 day rest period for grade 3 events and interrupt treatment for grade 4 events. • Discontinuation of treatment should be considered in cases of persistent severe hypertension, cardiac failure events, hand foot skin reaction, posterior reversible encephalopathy syndrome, or other complications of hypertension. Discontinue if the patient develops Grade 4 proteinuria (nephrotic syndrome). • **Missed dose / vomiting:** The next dose should be taken at the next scheduled time. • **Drug and food interactions:** Co-administration with herbal preparations containing St. John's wort is contraindicated. The inducing effect of St John's wort may persist for at least 2 weeks after stopping St John's wort. It is recommended that concomitant administration of tivozanib with strong CYP3A4 inducers, if used, should be undertaken with caution. Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure. Tivozanib inhibits the transporter protein BCRP *in vitro*, caution should be exercised if tivozanib is co-administered with rosuvastatin. • Tivozanib may cause fatigue/dizziness patients should be advised to take caution when driving or operating machinery. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
Reference(s)	SPC accessed online 21.04.2022 KMCC protocol RCC-009 V1 CDF List 1.210 accessed online 21.04.2022 BlueTeq form accessed online 21.04.2022

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 28 days

Day	Drug	Dose	Route	Administration Details
	TIVOZANIB	**1340 micrograms**	PO	OD for 21 days, followed by a 7-day rest period. Can be taken with or without food. The capsules must be swallowed whole with a glass of water and must not be opened. Available as 1340mcg and 890mcg capsules.
TTO	Drug	Dose	Route	Directions
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.