**Systemic Anti-Cancer Treatment Protocol**

# Axitinib

**PROTOCOL REF: MPHAAXITUR**
**(Version No: 1.1)**

**The protocol has been temporarily amended – please see the Oral SACT Operational Changes during Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.**

## Approved for use in:

An option for 2nd line treatment in advanced renal cell carcinoma with progression after previous TKI (tyrosine kinase inhibitor) or cytokine therapy

Performance status ≤ 1 (unless due to longstanding physical disability) without significant co-morbidity

## Dosage:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| Axitinib | 5mg twice daily | PO | Until progression or development of intolerable side effects |

Axitinib should not be used in patients with untreated brain metastases or recent active gastrointestinal bleeding.

Existing hypertension should be well controlled before starting treatment.

### Dose escalation

If the starting dose of 5mg twice daily is well tolerated for at least 2 consecutive weeks

- No adverse effects > grade 2

- Blood pressure < 150/90mmHg and
- No antihypertensives required

Then axitinib dose may be increased to 7mg twice daily.

Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily.

**Supportive Treatments:**

Domperidone 10mg three times a day when required

## Extravasation risk:

Not applicable

## Administration:

Available as 1mg, 3mg, 5mg and 7mg tablets.

Take with or without food approximately 12 hours apart, swallow whole with a glass of water.

**Drug interactions**

Axitinib is metabolized by the cytochrome CYP3A4/5 pathway and therefore drugs that induce or inhibit this enzyme should be avoided where possible.

**INDUCERS (lowers axitinib levels):** Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone

If co-administration is unavoidable, consider increasing axitinib dose gradually. If axitinib dose is increased, careful clinical monitoring is indicated. If co-administration with an enzyme inducer is stopped, reduce the axitinib dose immediately back to previous level.

**INHIBITORS (increases axitinib levels):** Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil.

A dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended by the manufacturers of axitinib.

The effect of strong inhibitors of CYP1A2 and CYP2C19 has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes (ciprofloxacin and other fluoroquinolones, fluvoxamine, moclobemide, verapamil, chloramphenicol and some herbal teas such as peppermint and chamomile).

## Main toxicities

The 'very common' (≥ 1/10) adverse reactions observed following treatment with axitinib are diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.

## Investigations and Treatment Plan:

| Cycle | Pre | C1 | C1 | C2 | C3 | Pre C4 | C4 | Ongoing |
|---|---|---|---|---|---|---|---|---|
| Week | | 1 | 3 | 5 | 9 | 12 | 13 | → |
| Medical Assessment | X | X | X | X | X | | X | Every 12 weeks |
| Nursing Assessment | | X | | X | X | | X | Every cycle |
| SACT assessment | X | X | | X | X | | X | Every cycle |
| FBC/ haematocrit | X | X | X | X | X | | X | Every cycle |
| U&E & LFTs | X | X | X | X | X | | X | Every cycle |
| Thyroid function | X | | | X | | | X | Every two cycles |
| CT scan | X | | | | | X | | Every 12 weeks |
| Informed Consent | X | | | | | | | First cycle only |
| Blood pressure measurement | X | X | X | X | X | | X | Every cycle |
| PS recorded | X | X | | X | X | | X | Every cycle |
| Toxicities documented | X | X | | X | X | | X | Every cycle |
| Weight recorded | X | X | | X | X | | X | Every cycle |
| Urine protein dipstick | As clinically indicated | | | | | | | As clinically indicated |
| ECG | As clinically indicated | | | | | | | As clinically indicated |

## Dose Modifications:

### Haematological Toxicity:

Proceed on day 1 if-

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| Plt ≥ 100 x $10^9$/L | ANC ≥ 1.0 x $10^9$/L |

If ANC < 1.0 x $10^9$/L or platelets less than 100 x $10^9$ defer for one week.

### Non-haematological toxicity

Dose increase or reduction is recommended based on individual safety and tolerability. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. Please refer to the Renal TKI Toxicity decision aid.

| **Axitinib** | |
|---|---|
| **Hypertension** | Patients should be screened for hypertension and controlled as appropriate.<br><br>During treatment, patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy according to NICE guidelines. The aim is to achieve a blood pressure below 140/90.<br><br>*Systolic 140-150 mmHg or Diastolic <90 mmHg:*<br>-Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary.<br><br>*Systolic 150-160mmHg or Diastolic 90-100mmgh:*<br>-Continue treatment at same dose.<br>-Repeat BP at GP, treatment needed if remained elevated or higher.<br>-Continue with vigilant BP monitoring until BP <140/90mmHg.<br><br>*Systolic 160-180 mmHg or diastolic 100-110 mmHg ( at least 2 readings 30 minutes apart):*<br>-Continue treatment at same dose<br>-Instigate BP treatment, to be reviewed at GP within 5 days.<br>-Continue with vigilant BP monitoring until BP <140/90mmHg. |

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| | *Severe hypertension (>200mmHg systolic or >110mmHg diastolic)* Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled.<br><br>The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management \| Guidance and guidelines \| NICE<br><br>Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes.<br><br>If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension. |
| Gastrointestinal disorders | Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain are the most commonly reported gastrointestinal adverse reactions.<br>**Diarrhoea:**<br>Grade 1 and 2 can be managed with supportive measures at home and with the use of anti-diarrhoea medication such as Loperamide 2mg after each stool if necessary. No treatment-break or dose changes required if symptom well controlled.<br>Grades 3 and 4 will need treatment interruption until improvement to Grade 1 or less. 1 step dose reduction is required when restarted.<br>Advise the patient to avoid any exacerbating foods and to eat small high carbohydrate meals. Also to drink plenty of water and to record the daily stool frequency.<br>Also to drink plenty of water and to record their daily stool frequency. **Severe presentation** may need admission if associated with any of the following: nausea/vomiting, cramping, fever, sepsis, neutropenia or dehydration.<br>**Nausea:** Domperidone is usually satisfactory. Nausea often settles with habituation to the drug. Administration of Sunitinib just before bedtime can help ameliorate this side-effect. |

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| **Hepatobiliary** | Hepatic changes reported in the form of raised bilirubin alanine aminotransferase (ALT), aspartate aminotransferase (AST) |
| **Perforations, fistulas, intra-abdominal abscesses.**<br><br>**Wound Complications** | Serious GI perforations and fistulas have been observed. Patients at risk should be evaluated carefully before commencing therapy.<br><br>Treatment should be stopped 24 hours prior to surgery |
| **Thromboembolic events** | Axitinib should be used with caution in patients who are at risk for, or who have a history of these events. |
| **Neurological** | Posterior reversible encephalopathy syndrome (PRES) neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Refer to toxicity management. |
| **Dermatological** | Palmar-plantar erythrodysaesthesia (hand-foot syndrome), rash |
| **Endocrinopathies** | hypothyroidism, hyperthyroidism |
| **Proteinuria** | Although commonly reported, this is not a common problem in clinical practice and regular screening/monitoring has low utility therefore should be performed when clinically indicated. |
| **Haematological** | Elevation of haemoglobin or haematocrit. An increase in red blood cell mass may increase the risk of embolic and thrombotic events.<br><br>Increase risk of haemorrhagic event. Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients.<br><br>Anaemia, Thrombocytopenia, Neutropaenia |

Please refer to ‘Renal Toxicity TKI Protocol’ for more information.

| **Recommended dose reductions** | |
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| First dose reduction | 3mg twice daily |
| Second dose reduction | 2mg twice daily |

## Hepatic impairment:

| Axitinib |
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| No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A).<br><br>A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily).<br><br>Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population. |

## Renal Impairment:

| Axitinib |
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| No dose adjustment is required. Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min. |

## References:

https://www.medicines.org.uk/emc/product/7948/smpc

Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Rini et al. (2011); Lancet 378:1931-1939

Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line Metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. Lancet Oncol 2013; 14:1233.

Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. NICE, national institute for health and clinical care and excellence. Technology appraisal guidance [TA333] Published date: 25 February 2015