

Axitinib Monotherapy

INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | *Reimbursement Status |
|---|-------|--------------|-----------------------|
| Treatment of adult patients with advanced renal cell carcinoma (RCC) after failure, on a previous line of therapy, i.e. treatment with SUNITinib , or a cytokine | C64 | 00104a | CDS |

**If the reimbursement status is not defined¹, the indication has yet to be assessed through the formal HSE reimbursement process.*

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.

The recommended dose of axitinib is 5mg twice daily. Treatment should continue as long as clinical benefit and/or radiologic response (RECIST version 1.1) is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments.

| Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---------|--|----------------|------------|
| Axitinib | 5 mg BD | PO (approximately 12 hours apart) with or without food swallow whole | N/A | Continuous |
| If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time | | | | |

ELIGIBILITY:

- Indications as above
- Adult patients with advanced renal cell carcinoma (RCC) of clear cell subtype after failure of prior treatment with sunitinib or a cytokine
- Two weeks or more since end of systemic treatment, four weeks for bevacizumab plus interferon-alfa
- ECOG performance status 0-2
- Adequate renal, hepatic and haematological organ function

USE WITH CAUTION:

Use with caution in patients:

- At risk of arterial and venous thrombotic events
- At risk of gastrointestinal perforation or fistula
- With significant recent myocardial infarction, uncontrolled angina or heart failure
- With CNS metastases
- With impaired hepatic function – see dose modification/exclusions
- Taking co-administered CYP3A4/5 inhibitors/inducers – see dose modification

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EXCLUSIONS:

- Hypersensitivity to axitinib or any of the excipients
- Pregnancy
- Breast feeding
- Uncontrolled hypertension
- Recent active gastrointestinal bleeding.
- Severe hepatic impairment (Child-Pugh class C)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Urinalysis for proteinuria,
- TFTs

Regular tests:

- FBC, renal and liver profile
- TFTs every 4 weeks
- Blood pressure weekly for 1st cycle then every 4 weeks
- Urinalysis for proteinuria should be repeated every 3 months

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.
- **Dose adjustment is not required on the basis of patient age, race, gender, or body weight.**
- **Dose increase:**
 - Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions > Grade 2 for two consecutive weeks may have their dose increased to 7 mg twice daily unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment.
 - 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.
- **Dose reduction:**
 - When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.
 - In the case of patients at higher doses (7 -10mg) reduction to the prior dose level.

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Haematological:

Table 1: Dose modification of axitinib in haematological toxicity

| ANC (x10 ⁹ /L) | | Platelets (x10 ⁹ /L) | Dose |
|---------------------------|-----|---------------------------------|-------|
| ≥ 1 | and | ≥ 75 | 100% |
| < 1 | Or | <75 | Delay |

Table 2: Dose modification of axitinib in Non-Haematological toxicity

| CTC-Grade | Dose |
|-----------|--|
| 1-2 | 100% |
| 3-4 | Delay until ≤ Grade 1 Dose reduce by 1 dose level |

In the case of patients at a dose of 5mg twice daily, one dose level reduction (dose level -1) is to a dose of 3mg twice daily.

A further dose reduction, i.e. dose level -2, is to a dose of 2mg twice daily.

In the case of patients at a higher dose (7-10mg twice daily) reduction is to the prior dose level.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

| Renal Impairment | Hepatic Impairment | |
|---|--------------------|-------------------|
| <ul style="list-style-type: none"> No dose adjustment is required. Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15ml/min. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required. The half-life of axitinib ranges from 2.5 – 6.1 hours. | Child Pugh Class | Dose |
| | A | 100% dose |
| | B | Reduce to 2 mg BD |
| | C | No information |

Management of adverse events:

Table 4: Dose Modification of axitinib for Adverse Events

| Adverse reactions | Discontinuation | Recommended dose modification |
|--|---|--|
| Proteinuria | | Reduce the dose or temporarily interrupt axitinib treatment |
| PRES | Temporarily interrupt or permanent discontinuation of treatment | |
| Co-administration of axitinib with strong CYP3A4/5 inhibitors (avoid where possible) | May require temporary or permanent discontinuation of therapy. | Reduce dose to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered. |
| Co-administration of axitinib with strong CYP3A4/5 inducers(avoid where possible) | May require temporary or permanent discontinuation of therapy. | A gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. If co- administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer. |

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS:

None Required

OTHER SUPPORTIVE CARE:

Diarrhoea is common, so provide a prescription for loperamide for new patients.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

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- **Cardiac failure:** Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.
- **Hypertension:** Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension, despite use of anti-hypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension. In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.
- **Thyroid dysfunction:** Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.
- **Arterial or venous embolic and thrombotic events:** Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial or venous embolic or thrombotic event within the previous 12 months.
- **Elevation of haemoglobin or haematocrit:** Increases in haemoglobin or haematocrit, may occur during treatment with axitinib. Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.
- **Haemorrhage:** 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. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.
- **Gastrointestinal perforation and fistula formation:** Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.
- **Wound healing complications:** Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

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- **PRES** In patients with signs or symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.
- **Proteinuria** Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Risk of drug interactions causing increased concentrations of axitinib with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit and grapefruit juice.
- Risk of drug interactions causing decreased concentrations of axitinib with CYP3A inducers.

ATC CODE:

Axitinib – L01XE17

REFERENCES:

1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; 378(9807): 1931-9.
2. Inlyta® Summary of Product Characteristics Accessed Oct 2018 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002406/WC500132188.pdf

| Version | Date | Amendment | Approved By |
|---------|------------|--|-------------------|
| 1 | 20/03/2013 | | Dr Derek Power |
| 2 | 17/10/2014 | Reformatted | Dr Derek Power |
| 3 | 21/10/2016 | Updated Adverse Reactions/Regimen Specific Complications to include information on Cardiac Failure and Haemorrhage as per SmPC | Prof Maccon Keane |
| 4 | 26/11/2018 | Updated to new NCCP template. | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at;

<http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/>

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