Pembrolizumab 200mg and Axitinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pembrolizumab in combination with axitinib for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.	C64	00583a	Reimbursement not approved[i]

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.

Pembrolizumab is administered every 21 days until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
Axitinib is administered twice daily continuously as long as clinical benefit is observed or until unacceptable toxicity occurs

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab[1]	200mg	IV	100ml 0.9% NaCl over 30minutes using a low protein binding 0.2-5µm in-line or add-on filter.	Every 21 days
Continuous	Axitinib[2]	5mg twice daily	PO	N/A	Continuous

[1]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml
[2]The dose should be taken approximately 12 hours apart with or without food swallow whole.
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:

- Indication as above
- Have histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features.
- Have locally advanced/metastatic disease (i.e., Stage IV RCC per American Joint Committee on Cancer) or have recurrent disease.
- Have received no prior systemic therapy for advanced RCC
- ECOG 0-2
- Adequate organ function

CAUTION:

Use with caution in patients:

- History of serious autoimmune disease
- At risk of arterial and venous thrombotic events
- At risk of gastrointestinal perforation or fistula
- With significant recent myocardial infarction, uncontrolled angina, heart failure, cerebrovascular event or TIA.

- With impaired hepatic function – see dose modification
- Taking co-administered CYP3A4/5 inhibitors/inducers – see dose modification

EXCLUSIONS:

- Patients with hypersensitivity to pembrolizumab, axitinib or any excipients
- Has had prior treatment with any anti-PD-1, or PD-L1, or PD-L2 agent.
- Has received prior therapy with VEGF/VEGFR or mTOR targeting agents. Note: Prior neoadjuvant/adjuvant therapy of these targeted agents is acceptable if completed > 12 months prior to treatment.
- Active CNS metastases and/or carcinomatous meningitis.
- History of interstitial lung disease or active non-infectious pneumonitis
- Any active clinically significant infection requiring therapy
- Poorly controlled hypertension defined as systolic blood pressure (SBP) ≥150mmHg and/or diastolic blood pressure (DBP)≥90mmHg.

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood pressure
- Glucose, TFTs
- Hepatitis B and C
- ECG

Regular tests:

- FBC, renal and liver profile, glucose
- Blood pressure
- TFTs
- ECG as clinically indicated

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.

Pembrolizumab

- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of pembrolizumab therapy and institution of systemic high-dose corticosteroid.

- Pembrolizumab dose reduction is not recommended.
- Guidelines for withholding of doses or permanent discontinuation of pembrolizumab are described below in Table 1
- Refer to Tables 1-8 for recommended dose modifications of pembrolizumab and axitinib.

Table 1: Recommended treatment modifications for pembrolizumab

Immune-related adverse reactions	Severity (NCI-CTCAE grading)	Treatment modification
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose>250mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	For dosing guidelines with liver enzyme elevations see table 6	
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold*
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome Any Grade 4 or recurrent Grade 3 immune-related adverse event	Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

Note: toxicity grades are in accordance with NCI-CTCAE v.4.

* until adverse reactions recover to Grade 0-1. If treatment related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab or if corticosteroid dosing cannot be reduced to ≤ 10mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.

Note: The safety of re-initiating pembrolizumab therapy in patients previously experiencing immune-related myocarditis and other immune related adverse events is not known.

Permanently discontinue pembrolizumab for for Grade 4 or recurrent Grade 3 adverse reactions, unless otherwise specified in Table 4 above

Axitinib

- The starting dose of axitinib is 5mg twice daily. The axitinib dose may be adjusted by a dosing interruption with or without dose reduction as indicated. The dose modification can occur independently for pembrolizumab and axitinib. Axitinib dose reductions are detailed in Table 2. Axitinib should be permanently discontinued if patients cannot tolerate 2mg twice daily.
- Patients who have tolerated axitinib 5mg twice daily for 2 consecutive treatment cycles (i.e. 6 weeks) with no > Grade 2 treatment-related adverse effects to axitinib and with blood pressure well controlled to ≤150/90 mmHg may have their axitinib dose increased to 7mg twice daily(Table 3).
- The dose of axitinib may be further increased to 10mg twice daily using the same criteria. Particular attention should be provided to a patient's overall safety profile prior to implementing a dose increase for axitinib.

Table 2: Dose reduction of axitinib

Dose level	Recommended dose
Starting dose	5mg Twice daily
Dose -1	3mg Twice daily
Dose -2	2mg Twice daily

Table 3: Dose increase of axitinib

Dose level	Recommended dose
Starting dose	5mg Twice daily
Dose +1	7mg Twice daily
Dose +2	10mg Twice daily

Haematological:

Table 4: Dose modification of axitinib in haematological toxicity

Grade	ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
Grade 1-3	0.5-1.5	and	25-75	100%
Grade 4	< 0.5	or	<25	Delay until recovery ≤Grade2 Restart axitinib dose reduced by 1 dose level Note: Grade 4 lymphopenia not associated with clinical events, (e.g, opportunistic infection) may continue on with axitinib

Non-haematological:

Table 5: Dose modification of axitinib in Non-Haematological toxicity

Adverse event	Grade	Recommendation
Hypertension	SBP ≤150mmHg and/or DBP≤100mmHg	Continue at the same dose level Antihypertensive treatment maybe initiated
	SBP>150mmHg but <160mmHg and/or DBP>100mmHg but <105mmHg	Continue at the same dose level, and institute new or additional antihypertensive medication if not on maximal antihypertensive treatment, or Reduce by 1 dose level if on maximal antihypertensive treatment.
	SBP>160mmHg and/or DBP>105mmHg	Hold dose until BP is <150/100mmHg and adjust antihypertensive medication. Restart with 1 dose level lower. Note: If axitinib dosing is temporarily interrupted, subjects receiving antihypertensive medications should be monitored closely for hypotension. The plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dose interruption.
	Recurrent hypertension following previous dose reduction	Repeat dose reduction by one lower dose level. Permanently discontinue if hypertension is severe and persistent despite anti-hypertensive treatments and dose reduction, or experiencing hypertensive crisis, transient or permanent neurological deficit related to uncontrolled hypertension.
Proteinuria	Dipstick negative or 1+ *If dipstick shows >1+, perform 24 hour urine protein or UPC. Dosing may continue while waiting for test results*	Continue at the same dose level
	Urine protein <3 g/24 hr or UPC < 3	Continue at the same dose level.
	Urine protein ≥3 g/24 hr or UPC ≥ 3	Hold until urine protein is <3g/24 hr. Restart with 1 dose level lower Permanently discontinue if urine protein cannot reduce to < 3g/24 hr after dose reduced to 2mg twice daily
Diarrhoea	Grade 1 – 2	Continue at the same does level
	Grade 3	Continue dose reduced by 1 dose level
	Grade 4	Follow the guidelines as in non-haematologic toxicities
Haemorrhage /Bleeding	Grade 1	For haemoptysis, interrupt study treatment and evaluate underlying causes. Resume at the discretion of the physician. For other Grade 1 haemorrhage/bleeding events, continue at the current dose; monitor as clinically indicated.

	Grade 2	For pulmonary or GI bleed (other than haemorrhoidal bleeding), permanently discontinue and follow-up per protocol. For other Grade 2 haemorrhage/bleeding events, interrupt study treatment until the AE resolves to ≤ Grade 1. Restart at 1 dose levellower
	Grade 3-4	Permanently discontinue
Hyperthyroidism	Grades 1-2	Continue at the same dose level
	Grade 3	If symptoms can be controlled with symptomatic medications, or if asymptomatic: may continue at the same dose level or dose may be reduced by 1 dose level as per physician's judgment
	Grade 4	Hold until recovery to Grade ≤ 1 or BL. Restart at 1 dose level lower.
Hypothyroidism	All grades	Axitinib can be continued while thyroid replacement therapy is instituted
Renal Failure or Nephritis	Grade 1-2	Continue at the same dose level
	Grade 3 -4	Hold until recovery to Grade < 2. Restart at 1 dose level lower.
Non-haematologic Toxicities, Laboratory Abnormalities and/or Other Drug Related Toxicities suspected to be contributed to axitinib and not considered immune-related	Grade 1 - 2	Continue axitinib at the same dose level
	Grade 3 - 4	Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry (other than LFTs) laboratory abnormalities may continue axitinib at the same dose level as per physician's judgment. Other Grade 3 toxicities may continue axitinib dose reduced by 1 dose level. Grade 4 asymptomatic biochemistry laboratory (other than LFTs) abnormality may continue axitinib without interruption as per physician's judgment. Other Grade 4 non-haematologic/laboratory and non-laboratory abnormalities: hold treatment until recovery to Grade <2, then restart axitinib dose reduced by 1 dose level.
	Grade 3- 4 discontinuation criteria	Permanently discontinue axitinib for: • Severe or Grade 3 drug-related AEs that recur • Any life-threatening AEs. • Subjects with the following events will be permanently discontinued: RPLS, arterial thrombosis/ischaemia

Table 6: Dose modification of pembrolizumab and axitinib for liver enzyme elevations

If ALT or AST ≥ 3xULN but < 10xULN without concurrent total bilirubin ≥ 2xULN	Withhold Pembrolizumab and axitinib until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered. If rechallenging with axitinib, dose reduction as per table 2 may be considered.
If ALT or AST ≥ 10xULN or > 3xULN with concurrent total bilirubin ≥ 2xULN	Permanently discontinue pembrolizumab and axitinib. Corticosteroid therapy may be considered.

Table 7: Concomitant use of axitinib and strong CYP3A4/5 inhibitors or inducers

Adverse reactions	Recommended dose modification
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 5mg twice daily to 2mg 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.

Renal and hepatic impairment:

Table 8: Dose modification of pemborlizumab and axitinib in renal and hepatic impairment

<table>
<tr><th></th><th>Renal impairment</th><th colspan="2">Hepatic impairment</th></tr>
<tr><td>Pembrolizumab</td><td>No dose adjustment is needed for patients with mild or moderate renal impairment.
Pembrolizumab has
not been studied in patients with severe renal impairment</td><td colspan="2">No dose adjustment is needed for patients with mild hepatic impairment. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment</td></tr>
<tr><td rowspan="4">Axitinib</td><td rowspan="4">No dose adjustment is required. Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/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.</td><td>Child Pugh Class</td><td>Dose</td></tr>
<tr><td>A</td><td>100%</td></tr>
<tr><td>B</td><td>The starting dose should be reduced from 5mg
twice daily to 2mg twice daily</td></tr>
<tr><td>C</td><td>No information – should not be used in this population</td></tr>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pembrolizumab	Minimal	(Refer to local policy).
Axitinib	Minimal to low	(Refer to local policy)

PREMEDICATIONS: No premedication is required for pembrolizumab in combination with axitinib.

OTHER SUPPORTIVE CARE:

Diarrhoea is common, so provide a prescription for loperamide for patients on axitinib

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Pembrolizumab

- **Immune-related adverse reactions:** Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.
  For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade≤1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
  Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤10mg prednisone or equivalent per day. Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones.
- **Immune-related pneumonitis**: Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.
- **Immune-related colitis:** Colitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 or recurrent Grade 3 colitis. The potential risk of gastrointestinal perforation should be taken into consideration.

- **Immune-related hepatitis:** Hepatitis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1mg/kg/day (for Grade 2 events) and 1-2mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued.
- **Immune-related nephritis**: Nephritis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis.
- **Immune-related endocrinopathies:** Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment. Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

  Hypophysitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and other causes excluded. Corticosteroids to treat secondary adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

  Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved.

  Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders.

  Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.
- **Immune-related skin adverse reactions:** Immune-related severe skin reactions have been reported in patients receiving pembrolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered .

  Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving pembrolizumab. For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for

assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued.
Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anti-cancer agents.

- **Other immune-related adverse reactions:** The following additional clinically significant, immune-related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis and encephalitis.
  Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10mg prednisone or equivalent per day.
  Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that recurs and for any Grade 4 immune related adverse reaction toxicity.
- **Infusion-related reactions**: Severe infusion-related reactions have been reported in patients receiving pembrolizumab. For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Axitinib:

- **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 or 6 months respectively
- **Elevation of haemoglobin or haematocrit:** Increases in haemoglobin or haematocritmay 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. Cases of ruptured aneurysms (including pre-existing aneurysms) have been reported, some with fatal outcome. Before initiating axitinib therapy in patients with pre-existing aneurysms, this risk should be carefully considered

- **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.
- **Posterior reversible encephalopathy syndrome (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:

- No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.
- Concomitant strong CYP3A4/5 inhibitors: Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations.
- Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Alert Card
https://www.hpra.ie/img/uploaded/swedocuments/c0984994-f8e8-4b10-95dd-7be12ff6c6f9.pdf

Patient Guide
https://www.hpra.ie/img/uploaded/swedocuments/896369cd-ec45-4e3a-978f-bacea851002e.pdf

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Version	Date	Amendment	Approved By
1	08/01/2020		Prof Maccon Keane
2	15/07/2020	Clarification of pembrolizumab treatment duration.	Prof Maccon Keane
3	22/01/2021	Amended dose modification in hepatic impairment (axitinib) and adverse effects	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Post 2012 indication. Not reimbursed through the ODMS or Community Drug Schemes (including the High Tech arrangements of the PCRS community drug schemes). Please check https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html for the most up to date reimbursement approvals.

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