PAZOPanib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
First line treatment of advanced Renal Cell Carcinoma (RCC) in adults and for patients who have received prior cytokine therapy for advanced disease.	C64	00445a	
Treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.	C49	00445b	

**If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not been 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.

PAZOPanib is taken once daily until disease progression or unacceptable toxicity develops (1 cycle=4weeks).

Drug	Dose	Route	Cycle
PAZOPanib	800mg once daily	PO Take without food at least one hour before or two hours after a meal	Continuous
PAZOPanib is available as 200mg and 400mg film-coated tablets These should be taken whole with water and not broken or crushed			

ELIGIBILTY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to PAZOPanib or to any of the excipients
- Severe hepatic impairment (bilirubin > 3 x ULN)

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood pressure
- ECG
- MUGA/ECHO if clinically indicated
- Thyroid Function

Regular tests:

- LFTs at weeks 1,2, 3and 4 and monthly thereafter or as clinically indicated
- FBC and renal profile monthly
- Blood pressure weekly for first 4 weeks and then monthly or as clinically indicated
- Thyroid function tests every 12 weeks
- Cardiac function 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.
- Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions.
- The dose of PAZOPanib should not exceed 800 mg.

Haematological:

Table 1: Dose modification of PAZOPanib for haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1	and	≥ 75	100%
<1	or	<75	Delay

Renal and Hepatic Impairment:

Table 2: Dose modification of PAZOPanib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Cr Cl (ml/min)	Dose	Bilirubin	Dose
≥30	100%	≤ 1.5 x ULN	800mg and monitor LFTs closely
<30	Caution is advised as there is no experience of PAZOPanib in this patient population.	1.5-3 x ULN	200mg and monitor LFTs closely
		>3 x ULN	Contra-indicated

Management of adverse events:

Table 3: Dose Modification of PAZOPanib for Non-Haematological Toxicity

CTC-Grade	Dose
1-2	100%
3-4	Delay until less than or equal to grade 1 Dose reduce by 1 dose level

Table 4: Dose modifications for PAZOPanib induced hepatotoxicity

Liver test values	Dose modification
Transaminase elevation between 3 and 8 x ULN	Continue on PAZOPanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
Transaminase elevation of >8 x ULN	Interupt PAZOPanib until transaminases return to Grade 1 or baseline. • If the potential benefit for reinitiating PAZOPanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce PAZOPanib at a reduced dose of 400 mg daily and measure serum liver tests weekly for 8 weeks. • Following reintroduction of PAZOPanib, if transaminase elevations > 3 x ULN recur, then PAZOPanib should be permanently discontinued.
Transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN	Permanently discontinue PAZOPanib. Patients should be monitored until return to Grade 1 or baseline. PAZOPanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 x ULN should be managed as per the recommendations outlined for isolated ALT elevations.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:
No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Hepatic effects**: Cases of hepatic failure (including fatalities) have been reported during use of PAZOPanib. Administration of PAZOPanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. PAZOPanib is not recommended in patients with severe hepatic impairment (total bilirubin > 3 x ULN regardless of any level of ALT) Exposure at a 200 mg dose is markedly reduced, though highly variable, in these patients with values considered insufficient to obtain a clinically relevant effect. In clinical studies with PAZOPanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed). In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Patients over 60 years of age may be at greater risk for mild (>3xULN) to severe (>8xULN) elevation of ALT. Patients who carry the HLA-B*57:01 allele have an increased risk of PAZOPanib-associated ALT elevations. Liver function should be monitored in all subjects receiving PAZOPanib, regardless of genotype or age (see Regular Tests).
- **Hypertension**: Patients with hypertension should exercise caution while on PAZOPanib. Blood

pressure should be well controlled prior to initiating treatment. Treatment with PAZOPanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and PAZOPanib dose reduction.

- **Cardiotoxicity:** The risks and benefits of PAZOPanib should be considered before beginning therapy in patients who have pre-existing cardiac dysfunction. The safety and pharmacokinetics of PAZOPanib in patients with moderate to severe heart failure or those with a below normal LVEF has not been studied. Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction. QT prolongation and Torsades de Pointes have also been reported. PAZOPanib should be used with caution in patients with any relevant cardiac history, or those taking anti-arrhythmics or other medicines that may prolong the QT interval. Ensure electrolytes are maintained within normal. When using PAZOPanib, base line and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within normal range is recommended.
- **Muscle pain:** Myalgias and muscle spasms can occur in patients treated with PAZOPanib
- **Hypopthyroidism:** Thyroid dysfunction in particular hypothyroidism may occur with this treatment. Monitor for signs and symptoms of thyroid dysfunction and manage as clinically appropriate.
- **Interstitial Lung Disease (ILD)/Pneumonitis**: ILD, which can be fatal, has been reported in association with PAZOPanib Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue PAZOPanib in patients developing ILD or pneumonitis.

DRUG INTERACTIONS:

- Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to PAZOPanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered.
- Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to PAZOPanib.
- Concomitant administration of PAZOPanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since PAZOPanib is an inhibitor of UGT1A1.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

PAZOPanib L01XE11

REFERENCES:

1. Sternberg CN, Davis ID, Mardiak J et al. PAZOPanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-1068.
2. van der Graaf WT, Blay JY et al. PAZOPanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879.
3. BCCA Protocol Summary for Palliative Therapy for Renal Cell Carcinoma Using PAZOpanib. Protocol Code UGUPAZO- Revised 1 Aug 2017

4. Votrient® Summary of Product Characteristics. Accessed Sept 2017 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001141/WC500094272.pdf

Version	Date	Amendment	Approved By
1	23/10/2017		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/