Pazopanib

Pazopanib (trade name **Votrient**) is a potent and selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumour growth and inhibits angiogenesis. It has been approved for renal cell carcinoma and soft tissue sarcoma by numerous regulatory administrations worldwide.[3][4][5][6]

1 Medical uses

It is approved by numerous regulatory administrations worldwide (including the FDA (19 October 2009), EMA (14 June 2010), MHRA (14 June 2010) and TGA (30 June 2010)) for use as a treatment for advanced/metastatic renal cell carcinoma and advanced soft tissue sarcomas.[2][3][4][5][6] In Australia and New Zealand, it is subsidised under the PBS and by Pharmac respectively, under a number of conditions, including:[7][8]

- The medication is used to treat clear cell variant renal cell carcinoma.
- The treatment phase is continuing treatment beyond 3-months.
- The patient has been issued an authority prescription for pazopanib
- The patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)
- This treatment must be the sole tyrosine kinase inhibitor subsidised for this condition.

It has also demonstrated initial therapeutic properties in patients with ovarian and non-small cell lung cancer,[9] though plans to apply to the EMA for a variation to include advanced ovarian cancer have been withdrawn and a license will not be sought in any country.[10][11]

2 Contraindications

The only contraindication is hypersensitivity to pazopanib or any of its excipients.[5] Cautions include:[2]

- Hypertension, including hypertensive crises reported
- QT interval prolongation and torsades de pointes reported.
- Thrombotic microangiopathy reported
- Thrombotic thrombocytopenic purpura reported
- Haemolytic uremic syndrome reported
- Haematologic parameter alterations reported in 31-37% of patients.
- Events of cardiac dysfunction (decreased LVEF and congestive heart failure) have been observed
- Fatal haemorrhage, arterial and venous thrombotic events and GI perforation have been observed in randomized clinical trials.

It has one black box warning by the US FDA, severe hepatotoxicity, including fatalities.[2]

3 Adverse effects

See also: List of adverse effects of pazopanib

The most common side effects of pazopanib are nausea, vomiting, diarrhoea (occurs in about half of patients), changes in hair colour, hypertension (which usually occurs during the first few weeks of treatment), appetite loss, hyperglycaemia, hypoglycaemia, electrolyte abnormalities (including hypocalcaemia, hypomagnesemia, hypophosphatemia), lab anomalies (including increased AST, ALT and protein in the urine), oedema, hair loss or discolouration, taste changes, abdominal pain, hypertension, rash, fatigue and myelosuppression (including leucopenia, neutropenia, thrombocytopenia and lymphopenia).[12] It has been associated with a low, but real risk of potentially fatal liver damage.[12]

4 Overdose

The treatment for overdose is purely supportive and the symptoms include grade 3 hypertension and fatigue.[5]

5 Interactions

Drug interactions include:[2]

- Coadministration with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, grapefruit juice) may increase pazopanib serum levels as it is a CYP3A4 substrate.
- CYP3A4 inducers (e.g. rifampin, carbamazepine) decrease pazopanib serum levels.
- It is a p-glycoprotein (PGP) substrate and hence PGP inhibitors such as quinidine may interact with pazopanib.
- Pazopanib is not a substrate for either of the hepatic OATP-1B1 and OATP-1B3.[13]
- Pazopanib have inhibitory potency towards OATP-1B1 but not for OATP-1B3.[14]

6 Mechanism of action

It is a multikinase inhibitor, with c-KIT, FGFR, PDGFR and VEGFR being amongst the inhibited enzymes.[2][12][15][16][17][18]

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