NEW DRUGS

New drugs

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Cabozantinib

Approved indication: renal cell carcinoma

Cabometyx (Ipsen)
20, 40 and 60 mg film-coated tablets
Australian Medicines Handbook section 14.2.4

Cabozantinib is a small molecule inhibitor of a number of tyrosine kinases that are thought to be involved in tumour growth and angiogenesis. It is indicated for patients with renal cell carcinoma that has progressed after being treated with a vascular endothelial growth factor receptor inhibitor such as sorafenib,[1] pazopanib[2] or axitinib.[3]

The approval of cabozantinib is based on an open-label phase III trial of 658 pre-treated patients with advanced disease. They were randomised to receive cabozantinib 60 mg or everolimus 10 mg once daily. Median progression-free survival (7.4 vs 3.9 months) and overall survival (21.4 vs 16.5 months) were longer with cabozantinib than with everolimus. The objective response rate (proportion of patients with a partial response) was also higher for cabozantinib (17% vs 3%) (see Table).[4,5]

The median duration of treatment with cabozantinib was 8.3 months. Dose reductions and interruptions were needed in 62% and 12% of patients.[5] Adverse events were very common – the most frequently reported were diarrhoea (74%), fatigue (56%), nausea (50%), anorexia (46%), palmar-plantar erythrodysaesthesia (42%), hypertension (39%), vomiting (32%), weight loss (31%) and constipation (25%). Over two-thirds of patients had a serious adverse event.[5] These included gastrointestinal perforation and fistulas, QT prolongation, haemorrhage and pulmonary embolism. Wound complications can also occur and cabozantinib should be stopped at least four weeks before scheduled surgery.

The recommended dose of cabozantinib is 60 mg once a day. This should be reduced to 40 mg once daily in patients with mild–moderate hepatic impairment. The drug should be used with caution in people with mild–moderate renal impairment and is not recommended for those with severe hepatic or renal impairment.

Patients should be advised not to eat for at least two hours before and one hour after taking cabozantinib. Following an oral dose, peak plasma concentrations are reached within 2–3 hours. The plasma half-life of cabozantinib is 99 hours and the drug and its metabolites are excreted in the faeces (54%) and urine (27%).

Cabozantinib is highly protein bound and there is a theoretical risk that it will displace concomitant warfarin so INR monitoring is recommended.

Cabozantinib is a substrate of cytochrome P450 (CYP) 3A4 so co-administration of strong inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicin) increase and decrease cabozantinib concentrations respectively. Caution is therefore urged and long-term use of inhibitors and inducers should be avoided. Cabozantinib also inhibits P-glycoprotein in vitro and may increase concentrations of co-administered substrates such as dabigatran, digoxin, maraviroc, saxagliptin and tolvaptan.

Cabozantinib offers another option for patients who have relapsed renal cell carcinoma. In the trial, it prolonged overall survival for up to five months longer than everolimus. However, serious adverse effects are very common with cabozantinib and are likely to limit treatment. The drug is also approved overseas for medullary thyroid cancer.

T manufacturer provided the product information

Table **Efficacy of cabozantinib in advanced renal cell carcinoma**

	Cabozantinib 60 mg/day (330 patients)	Everolimus 10 mg/day (328 patients)
Median progression-free survival	7.4 months	3.9 months
Objective response rate (proportion of patients with a partial response)	17%	3%
Median overall survival	21.4 months	16.5 months

Based on reference 5

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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REFERENCES

1. Sorafenib tosylate. Aust Prescr 2006;29:167-71. https://doi.org/10.18773/austprescr.2006.103
2. Pazopanib. Aust Prescr 2010;33:193-8. https://doi.org/10.18773/austprescr.2010.094
3. Axitinib for renal cell carcinoma. Aust Prescr 2012;35:208-10. https://doi.org/10.18773/austprescr.2012.092
4. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814-23. https://doi.org/10.1056/NEJMoa1510016
5. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-27. https://doi.org/10.1016/S1470-2045(16)30107-3

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.