

Cabozantinib: a novel tyrosine kinase receptor inhibitor for the treatment for advanced renal cell carcinoma

Abstract

Cabozantinib is under universal development with Exelixis Corporation, was approved by the U.S. Food and Drug Administration to treat patients with advanced renal cell carcinoma in patients who have been treated previously with antiangiogenic therapy. It inhibits possible activity of receptor tyrosine kinases (RTKs). This manuscript reviews the available information on cabozantinib with respect to its pharmacodynamics and pharmacokinetics.

Keywords: cabozantinib, pharmacodynamic, pharmacokinetics

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Abbreviations: ARCC, advanced renal cell carcinoma; FDA, food and drug administration; VEGFR, vascular endothelial growth factor receptor; MET, mesenchymal-epithelial transition; FMS, like tyrosine kinase 3; RTKs, receptor tyrosine kinases

Introduction

Advanced renal cell carcinoma (ARCC) is the most familiar type of kidney tumor.¹ Cabozantinib (Cabometyx TM, XL184) is a novel FDA approved drug and it is used for treatment of advanced renal cell carcinoma in patients who have been treated previously with antiangiogenic therapy² and was developed by Exelixis Inc. In adults, Cabozantinib also has been approved for the management of ARCC in Europe.³

Molecule

Cabozantinib is an orally active drug with a molecular weight of 501.51g/mol and molecular formula of C₂₈H₂₄FN₃O₅. The structure of cabozantinib is given in Figure 1. The chemical structure name is N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide.⁴

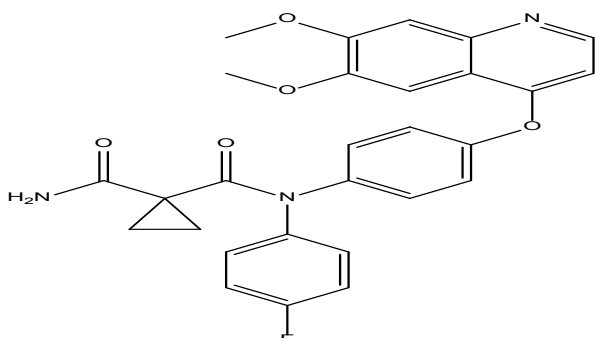


Figure 1 The structural formula of Cabozantinib.

Pharmacodynamics

Cabozantinib acts by inhibiting possible activity of receptor tyrosine kinases (RTKs) under attacked at vascular endothelial

growth factor receptor types 1 (VEGFR-1), 2 (VEGFR-2) and 3 (VEGFR-3), mesenchymal-epithelial transition factor (MET) but also inhibits the action of many other factors such as FMS-like tyrosine kinase 3 (FLT-3), TIE-2, ROS1, MER and RET.^{4,5} Various features and properties of cabozantinib are listed in Table 1.

Randomized study design

A phase 3 trial, randomized study, funded by Exelixis (clinical trials no. NCT01865747), was designed to study the efficacy of cabozantinib. Total 658 random recipients were selected to receive the recommended daily dose of cabozantinib 60 mg. The end point of study selected was median progression free survival. The results showed approximately 7.8 months, median progression free survival with a lower death rate of approximately 42%. The study also supported a longer overall survival of the patient (statistically supported). The adverse effects of the drug were managed with a reduction in the doses.³

Pharmacokinetics

Absorption: Cabozantinib is an orally active compound, showing the peak plasma concentrations at 5 hrs, the plasma half-life of it was 91.3±33.3 hrs. The middle time to achieve C_{max} was found 3–4hrs.

Administration of cabozantinib with rifampin showed in upper plasma clearance (4.3-fold higher) and reduce in plasma AUC_{0–inf} of cabozantinib approximately 77%, but administered with the co-administration of ketoconazole, it was obtained that plasma clearance was decreased (29%) or AUC_{0–inf} was increased (38%). It does not show significant effect on rosiglitazone maximum plasma concentration (C_{max}), AUC_{0–24}, or AUC_{0–inf}. The apparent oral clearance (CL/F) of cabozantinib was found to be 106 L/day. Cabozantinib showed expected effective half-life (t_{1/2}) around 55 hrs.^{6–8}

Distribution: At steady state, the mean apparent volume of distribution of cabozantinib is 349 L. The plasma protein binding of cabozantinib is very high (≥99.7%).⁹

Metabolism: Cabozantinib is metabolized in the liver. Cytochrome P450 (CYP) 3A4 is the primary CYP isoenzyme and responsible for

metabolism of cabozantinib and it inhibits CYP2C8. Monohydroxy sulfate is the major metabolite of it.⁷

Elimination: Cabozantinib and its metabolites are primarily excreted by the kidneys. Total mean radioactivity recovery was found to be 81.09% in 48 days. Approximately 27.29 % and 53.79 % of the radioactive dose of cabozantinib was eliminated in urine and feces.⁹

Recommended dose: The recommended dose of cabozantinib for the treatment of advanced renal cell carcinoma is 60 mg. Patients should be aware not to administer the drug with foods (citrus fruits or juice, nutritional supplements, etc.) as it may inhibit cytochrome P450 during treatment.²

Special instructions: An important instruction must be provided to the patients regarding its administration. Food and other supplements should not be taken before 2 hours and at least one hour after taking cabozantinib.²

Table 1 Some main properties of Cabozantinib

Features and properties of Cabozantinib	
Alternative names	Cabometyx™, XL184, Cometriq
Class	CYP3A4 inhibitor
Mechanism of Action	Receptor tyrosine Kinases, VEGFR-1, VEGFR-2, VEGFR-3, MET, FLT-3, TIE-2, ROSI, MER and RET inhibitor
Route of Administration	Oral
Pharmacokinetic	Rapid, dose proportional absorption after oral administration, maximum plasma concentration (C_{max}) is 3–4 hrs, bound to plasma proteins, T_{max} 91.3±33.3 hrs, Half life is 55 hrs Approximately 27.29 % and 53.79 % of Cabozantinib was eliminated in urine and feces
Adverse events Most frequent (incidence > 5 %)	Fatigue, diarrhea, weight loss, and transminitis
ATC Code	L01XE26
Pharmaceutical Form	Tablet, Capsule
Chemical Name	N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide
Molecular Formula	$C_{28}H_{24}FN_3O_5$
Molecular Weight	501.51 g/mol

VEGFR, vascular endothelial growth factor receptor; MET, mesenchymal-epithelial transition; FLT-3, FMS-like tyrosine kinase 3

Conclusion

Cabozantinib's approval was based on the results of a phase III randomized clinical trial comparing the drug with everolimus, which the FDA approved in 2009 for patients with kidney cancer whose disease has progressed after prior treatment.

It is concluded that cabozantinib is an orally active and new anticancer (kinase inhibitor) drug. Cabozantinib was approved for patients with ARCC, previously treated with antiangiogenic therapy by the U.S. Food and Drug Administration (U.S.FDA). Cabozantinib is a novel probable standard of care for the patients of ARCC.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

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