# TDM monograph cabozantinib

## Synonyms: Cometriq, Cabometyx

## Summary

| | |
|---|---|
| **Indication:** | Registered indications:<br>Progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (Cometriq®))<br><br>Locally advanced or metastatic differentiated thyroid carcinoma (Cabometyx®)<br><br>Hepatocellular carcinoma, following treatment with sorafenib (Cabometyx®)<br><br>Advanced renal cell carcinoma (Cabometyx®):<br>- as first-line treatment, in patients with intermediate or poor risk<br>- as first-line treatment in combination with nivolumab<br>- as second-line treatment, following treatment with a VEGF-inhibiting tyrosine kinase inhibitor.<br><br>Unresectable or metastatic pancreatic neuroendocrine tumours (pNET) and extra-pancreatic neuroendocrine tumours (epNET) (Cabometyx®) |
| **Sample material:** | Plasma |
| **Time of sampling:** | Through concentration (at least 6 hours after administration), 4 weeks after initiation of therapy or dose adjustments. |
| **Storage conditions:** | 2-8 °C, transport at room temperature |
| **Interpretation:** | Higher concentrations are associated with increased effectiveness as well as a higher risk of toxicity, with substantial overlap in exposure ranges. Therefore, TDM results should be interpreted in combination with clinical response and tolerability rather than using concentration thresholds in isolation. |
| **Evidence level:** | 2 |

## Contents



## Introduction

Cabozantinib is a tyrosine kinase inhibitor of MET (hepatocyte growth factor receptor) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2. It is registered for treatment of renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), thyroid carcinoma and neuroendocrine tumors. There is an association between cabozantinib exposure and effectiveness and toxicity.

## Dosing guidelines

See Cabozantinib | KNMP Kennisbank. Cabozantinib is available in two non-interchangeable formulations: Cometriq (capsules) and Cabometyx (tablets). The approved indications and dosing regimens differ between the two products.

Cometriq is approved exclusively for the treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC) and is started at a standard dose of 140 mg per day.[1]

Cabometyx, in contrast, is approved for RCC, HCC, and locally advanced or metastatic differentiated thyroid carcinoma and is registered with a starting dose of 60 mg per day. In clinical practice, however, lower starting doses (40 mg) are frequently used due to the high incidence of dose-dependent toxicity associated with the registered dose.[2,3]

The two formulations are not interchangeable. Although their AUC differs on average by only 8%, the tablet's Cmax is, on average, 19% higher. Importantly, the upper bound of the 90% confidence interval for

Cmax reached 132%, exceeding the standard bioequivalence range of 80–125%. Therefore, bioequivalence was not established, and the two formulations should not be substituted for one another.[4]

## Indications/Criteria for TDM

Therapeutic drug monitoring (TDM) of cabozantinib is classified as evidence level 2. Routine monitoring is not recommended as dosing should primarily be titrated to the maximum tolerated dose up to 60 mg once daily for Cabometyx or 140 mg once daily for Cometriq.[5] TDM may be considered in clinical situations when therapeutic response is inadequate, tolerability issues are encountered or comorbidities/comedication may lead to altered drug exposure levels. These situations include altered pharmacokinetics due to organ dysfunction, bariatric surgery, extreme obesity, unavoidable drug–drug interactions, suspected non-adherence to therapy, or to guide dose adjustments in the event inefficacy or toxicity.

## Reference values

Higher cabozantinib trough concentrations are associated with improved clinical effectiveness.[6] Increased exposure is also associated with a higher risk of toxicity. The exposure ranges associated with effectiveness and toxicity overlap[5-10] Therefore, cabozantinib concentrations should always be interpreted in combination with clinical response and tolerability when considering dose adjustments. The table below integrates exposure, treatment response, and toxicity to support therapeutic drug monitoring–guided dosing decisions.[5]

| Exposure (ng/mL) | Toxicity | Response | Recommendation |
|---|---|---|---|
| < 750 | Manageable/absent | - | Consider to increase the dose |
| > 500 | Manageable | + | No dose adjustment |
| > 500 | Non-manageable | + | Reduce the dose |
| < 500 | Non-manageable | - | Switch to alternative |

### Efficacy

Several studies have reported associations between cabozantinib exposure and clinically relevant efficacy endpoints. The available evidence is summarized below by indication.

**Metastatic RCC (monotherapy)**

Most evidence on the exposure-response relationship for cabozantinib has been derived from studies in patients with mRCC receiving cabozantinib monotherapy. In the phase 3 METEOR trial, a nonlinear exposure-response relationship was observed: increasing the dose did not result in proportionally greater clinical benefit, indicating a plateau in the exposure-response curve. A daily dose of 60 mg (median plasma concentration: 1125 ng/mL) demonstrated slightly greater efficacy than the 40 mg dose (750 ng/mL; hazard ratio [HR] for progression or death: 1.1) and markedly greater efficacy than the 20 mg dose (375 ng/mL; HR: 1.4). Based on these findings, a starting dose of 60 mg once daily was approved for mRCC.[6]

Two observational studies investigated whether exposures >750 ng/mL were associated with improved outcomes.[5,8] While no clear efficacy benefit was demonstrated at this threshold, both studies confirmed a concentration-effect relationship. In the first study (n=78), patients with a Cmin>336 ng/mL (lowest decile) had longer PFS compared to those below this level (11.3 vs. 4.9 months; p=0.025), although no association with overall survival (OS) was found.[8] In the second study (n=59) a Cmin above the median of 572 ng/mL

was associated with a numerically non-significant longer PFS compared to patients with Cmin below 572 ng/mL: 65 weeks (95% CI: not reached) vs. 42 weeks (95% CI: 20–64), respectively (p = 0.055).[5]

Several observational studies have further evaluated the exposure-response relationship. In a study the investigators attempted to determine a cut-off point for effectiveness. In this study, involving 76 patients, a Ctrough threshold of 536 ng/mL was identified, yielding 64.3% sensitivity and 73.5% specificity for detecting disease progression.[10] This threshold was confirmed in a small cohort of 10 Japanese patients.[11] The threshold suggests a moderate ability to predict disease progression based on plasma concentration, but its clinical utility remains limited due to suboptimal sensitivity and specificity.

Furthermore, the feasibility of cabozantinib TDM was evaluated in a prospective study from the Dutch Pharmacology Oncology Group. The cohort was closed prematurely due to inability to achieve the target concentration of 750 ng/mL. Patients in this study started on 40 mg once daily (median exposure 696 ng/ml). Twenty of the 25 patients had at least one concentration below 750 ng/mL, however interventions were only possible in 5 patients. In all other patients, dose escalation was not feasible due to adverse events.[12]

**mRCC (in combination with nivolumab)**

In the phase 3 CheckMate 9ER trial evaluating the combination of cabozantinib and nivolumab in patients with mRCC, no relationship was observed between exposure quartiles and either PFS or OS. The investigators recommended an initial cabozantinib dose of 40 mg, with subsequent dose reductions based on adverse events.[13]

**HCC**

For HCC in the CELESTIAL phase three study, an association between dose and both OS and PFS was found. When expressed relative to the 60 mg dose (corresponding to 1148 ng/mL), the predicted HRs for death (95% CI) were 1.20 (0.79–1.78) for 40 mg (766 ng/mL) and 1.43 (1.09–1.85) for 20 mg (383 ng/mL), indicating reduced efficacy at lower starting doses compared with 60 mg.[14] In a real-world evaluation with 34 Japanese patients, the exposure-response relationship was not found, there was no difference between PFS or OS between patients treated with ≥40 mg or 20 mg.[15]

**MTC**

In the Cosmic-311 study in 115 patients with refractory differentiated thyroid cancer no association between average cabozantinib exposure and PFS was found when exposure was divided in tertiles. Notably, the exposure in all tertiles was relatively high compared to other indications (median exposure 1$^{st}$ tertile 615.1 ng/ml, 2$^{nd}$ tertile 889.5 ng/ml, 3$^{rd}$ tertile 1254 ng/ml).[16]

## Relationship with occurrence of side effects & toxicity

Toxicities related to cabozantinib are common and the incidence increases with higher doses. In clinical trials for mRCC, where patients were treated with 60 mg once daily, between 46% and 62% of patients required dose reductions due to toxicity and between 39% and 68% experienced adverse events grade 3 or higher. The most frequent dose-dependent toxicities include hand-foot syndrome (HFS), hypertension, fatigue, and diarrhea.[17,18]

Data from the METEOR trial showed that the 60 mg dose (with a steady-state average concentration of 1,125 ng/mL) compared to the 40 mg dose (750 ng/mL) resulted in increased HRs for toxicity: 1.49 for HFS, 1.42 for fatigue, 1.36 for hypertension, and 1.33 for diarrhea. The 20 mg dose (375 ng/mL) had lower risk of

adverse events compared to 40 mg, with HRs of 0.67 for HFS, 0.70 for fatigue, 0.74 for hypertension, and 0.75 for diarrhea.[6,7]

These results were confirmed in other populations. The CELESTIAL trial in patients with HCC also demonstrated a relationship between dose and adverse events. Compared to 40 mg, HRs for HFS were 0.47 (20 mg) and 1.52 (60 mg); for diarrhea, 0.71 (20 mg) and 1.16 (60 mg); and for hypertension, 0.61 (20 mg) and 1.32 (60 mg).[14] Similarly, in the CheckMate 9ER trial, where patients with mRCC were treated with combined nivolumab and cabozantinib, the 20 mg dose (average plasma concentration of 386 ng/mL) showed HRs of 0.63 for HFS and 0.48 for diarrhea compared to the 40 mg dose (772 ng/mL).[13]

Several observational studies have also demonstrated an exposure-toxicity relationship, confirming that higher exposure levels are associated with increased toxicity in real-world settings. In a population of mRCC patients (n=76), the patients experiencing severe (Grade 3-4) or clinically relevant (Grade 2 requiring dose reduction) toxicity, had significantly higher mean trough concentrations (950 ng/mL) compared to patients without toxicity (574 ng/mL).[10] They identified a trough concentration threshold of 618 ng/mL, which predicted relevant toxicity with moderate sensitivity (63%) and specificity (65%). In a study with 47 patients (25 with mRCC and 22 with salivary gland carcinoma from a phase II study), the ones who required dose reductions had higher median trough concentrations (831 ng/mL) compared to those who did not require reductions (569 ng/mL).[19]

Two studies with mRCC patients investigated the association between concentrations above 750 ng/ml and dose reductions. In the first study (n=59) dose reductions were more prevalent in patients with concentrations ≥750 ng/ml (78.6% vs 38.7%, p = 0.003).[5] Similar results were found in the second study (n=78). A cut-off for Caverage of 750 ng/mL resulted in more dose-related toxicity (69% vs 35%, respectively; p = 0.006).[8] These studies indicate no absolute concentration threshold, as tolerability varies among individuals; however, levels above ~750 ng/mL are linked to a higher risk of clinically significant toxicity.

## Sampling & storage conditions

Trough concentrations are preferred for therapeutic drug monitoring of cabozantinib, but its long terminal half-life makes precise sample timing less critical. Samples should be drawn no earlier than 6 hours after the last dose to ensure absorption is largely complete. For samples drawn 6–12 hours post-dose, extrapolate the measured concentration to the trough using cabozantinib's half-life.
Due to the long half-life steady state is reached after approximately 4 weeks.[3] Sampling for TDM should preferably occur after steady state has been achieved.

Cabozantinib is stable in plasma at 4-8 ℃ or room temperature for 14 days.[20] Plasma samples may be transported at room temperature without compromising stability.[21]

## Background information

### Pharmacodynamics

Cabozantinib targets multiple receptor tyrosine kinases involved in tumor growth, angiogenesis, pathological bone remodeling, drug resistance, and metastatic cancer progression. It primarily inhibits MET and VEGF receptors. In addition, cabozantinib blocks other tyrosine kinases including AXL (GAS6 receptor), RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3, and TIE-2. In various preclinical tumor models,

cabozantinib demonstrated dose-dependent tumor growth inhibition, tumor regression, and/or suppression of metastasis.

## Pharmacokinetics

Absorption: Cabozantinib is well absorbed with a Tmax at approximately 2-5 hours for Cometriq and 3-4 hours for Cabometyx. Multiple peaks present in the plasma concentration–time profiles after a single oral dose suggest that cabozantinib is enterohepatically recirculated or has delayed or multiple sites of absorption.[4] A high-fat meal significantly increases cabozantinib systemic exposure, with the AUC increasing by 57% and Cmax by 40%. Co-administration of a proton pump inhibitor (esomeprazole) did not result in a clinically meaningful change in cabozantinib plasma exposure.[22]

Distribution: Cabozantinib is highly protein bound (approximately 99.65% to 99.79%) in plasma. The free fraction is correlated with serum albumin concentration. Volume of distribution of the central compartment (Vc/F) was 212 L. The inter individual variability (expressed as percentage coefficient of variation) for Vc/F was 67%.[3,23]

Metabolism: Cabozantinib undergoes extensive metabolism, with CYP3A4 as the primary enzyme responsible for metabolism.

Elimination: The plasma terminal half-life was ~110 hours, and mean steady-state clearance (CL/F) was 2.48 L/hr. The Inter-individual variability in CL/F was ~46%. After a single 14C-cabozantinib dose, ~81% of radioactivity was recovered over 48 days; 54% in feces and 27% in urine.[4,23,24] Patients with MTC had approximately 93% higher CL/F relative to healthy volunteers, resulting in 40–50% lower predicted steady-state cabozantinib plasma concentrations.[25]

Renal impairment: No dose adjustments are recommended for patients with renal impairment. Renal elimination is a minor route of elimination for cabozantinib. The cabozantinib exposure (AUC0-∞) observed in mildly and moderately renally impaired cohorts is only 30% and 7 % increase compared to patients without renal impairment.[26]

Hepatic impairment: The hepatobiliary pathway appears to be the main route of elimination for cabozantinib and its metabolites. For healthy volunteers with mild hepatic impairment the cabozantinib AUC was 81% higher and for moderate hepatic impairment 63% compared to healthy individuals. The lower effect in patients with moderate hepatic impairment has been suggested to result from a decrease in protein binding.[26] However, the effect hepatic impairment on the pharmacokinetics of cabozantinib observed in healthy volunteers was not replicated in patients with malignancies.[23] In patients with mild hepatic impairment, population pharmacokinetic analyses predicted minimal differences in CL/F compared with patients with normal hepatic function. The limited number of patients with moderate or severe hepatic impairment precluded dosing recommendations for these subpopulations.[23] The observed differences between patients and healthy individuals are likely due to distinct underlying causes. In non-malignant patients, elevated liver enzymes are primarily indicative of hepatic impairment. In patients with malignancies, elevated liver enzymes are more commonly attributed to liver-metastasis. For dose adjustments, in patients with Child-Pugh Class A/B (mild to moderate impairment), a starting dose of 66% of the original dose is recommended, with the option to increase if tolerated. For patients with Child-Pugh Class C (severe impairment), treatment with cabozantinib is not recommended.[27]

### Pharmacogenetics

There are currently no clinically relevant drug-gene interactions for cabozantinib known.

## Interactions

Cabozantinib is substrate for CYP3A4 combination with strong CYP3A4 inhibitors can increase the cabozantinib exposure. For example, combination with the strong CYP3A4 inhibitor ketoconazole increased cabozantinib exposure by 39%. Combination of cabozantinib with the strong CYP3A4 inducers can reduce the cabozantinib exposure. For example, rifampicin reduced cabozantinib exposure by 77%.[28]

Bile acid sequestrants like cholestyramine may reduce absorption, however the clinical relevance is unknown.[3]

## PK parameters

| | **F** (%) | **Cl/F** (L/h) | **Vd/F** (L/kg) | $t_{1/2}$ ($h^{-1}$) | Protein binding | Tmax (h) | Ref. |
|---|---|---|---|---|---|---|---|
| Adults | ND | 2.48 | 212 | 110 | 99.7% | 3-4 | [3] |

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## Colophon

This guideline has been constituted by dr. E. Leegwater (hospital pharmacist i.t.), dr. E. Boerrigter (hospital pharmacist-clinical pharmacologist) and prof. dr. N.P. van Erp (hospital pharmacist-clinical pharmacologist) under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
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## Appendices

Not applicable