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Cabozantinib: cabometyx versus cometriq. Are they interchangeable?

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***Abstract*--** Cabozantinib is an oral multi-tyrosine kinase inhibitor that targets vascular endothelial growth factor (VEGFR), mesenchymal epithelial transition factor (MET) and AXL. Cabozantinib is used for treating different types of cancer. It is available in the market in two different dosage forms with two different trade names. Cabometyx (cabozantinib) is available as 20mg, 40mg and 60mg film coated tablets and is approved by FDA for the management of renal cell carcinoma and hepatocellular carcinoma. However, cometriq (cabozantinib) is available as 20mg and 80mg capsules and is approved by FDA for treatment of thyroid cancer. Availability of two dosage forms for cabozantinib with different trade names for different indications is considered as potential for confusion and prescribing error. Implementation of good prescribing practice is essential in this case. Successive governments have promoted the prescribing of drugs by generic rather than the trade name. Some drugs should not be prescribed generically for different reasons, for example when dosage forms of the products are not pharmaceutically equivalent. Cabozantinib is an example for this scenario. Cabometyx and cometriq are not bioequivalent. In conclusion, each institution should have a generic prescribing policy. This policy must include drugs that cannot be prescribed generically. Based on posology, cabometyx and cometriq should not be used interchangeably but in case a patient must switch from cabozantinib capsules to cabozantinib tablets, the patient should continue with cabometyx using a dose not exceeding 60mg or to continue with the current cometriq dose whichever is lower. Do NOT substitute cabometyx tablets with cometriq capsules.

Keywords: Cabozanitinib, Cabometyx, Cometriq, Pharmacokinetics, Interchangeable

1. INTRODUCTION

Cabozantinib is a multi-tyrosine kinase inhibitor approved by FDA and available in the market in two dosage forms. Cabometyx (cabozantinib) is available as 20mg, 40mg and 60mg film coated tablets and cometriq (cabozantinib) is available as 20mg and 80mg capsules. Each dosage form is approved by FDA for a different indication.

Availability of cabozantinib in the market as two different trade products while being approved by FDA for different types of cancer is considered as potential source of confusion and prescribing error among healthcare professionals. Prescription errors could be minor and harmless or might result in life threatening situations.

This article is of significant importance for daily clinical practice as it clarifies the difference between cabometyx and cometriq, mainly for healthcare professionals dealing with oncology patients in order to avoid medication errors and ensure patient safety.

2. GENERIC PRESCRIBING PRACTICE

Generic prescribing is promoted in many countries as an indicator of good prescribing practice. Using the generic name means prescribing the drug using its active ingredient rather than its brand name. There are many reasons to prescribe drugs using generic rather than brand names, such as difficulty to remember different brand names, no need to remember which brand is currently subsided, less potential for confusion among healthcare professionals and medication errors, in addition to the use of less expensive medication brands more often, pharmacists can dispense the medication in stock without a need for consultation and providing a guide to the drug's pharmacology and chemical class, all which can be performed easier using the generic name [1-3].

It is not always possible to prescribe generically. Brand names should be used where it is clear that prescribing generically will lead to confusion for the dispending drug or create problems with bioavailability. This scenario applies in the following situations [1-6]:

1. The product is modified release: substitution of a modified release product with standard release formulations might not be advisable once treatment started as the composition and pharmacokinetics are difficult to standardize. This applies to some drugs as theophylline and isosorbide mononitrate.
2. The product has a narrow therapeutic range: in drugs with an efficacy and/or toxicity that are critically dependent on plasma concentration, the allowable differences in bioavailability between the reference and generic product

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in bioequivalence testing may result in changes in clinical effect between brands, although this is unlikely. Examples for such products are lithium carbonate and ciclosporin.

3. The delivery systems or dosage forms of the products are not pharmaceutically equivalent: e.g. cabometyx tablets and cometriq capsules, both products have the same active ingredient which is cabozantinib but they are not bioequivalent.
4. Combined preparations: e.g. hormone replacement therapy and oral contraceptive.
5. The same drug is used for different and separately branded indications: for example, cabometyx is approved for RCC and HCC and cometriq is approved for MTC. Both brands have cabozantinib as active ingredient.

3. CABOZANTINIB FDA APPROVED INDICATIONS

Table 1. Cabozantinib approved indications

Drug name	Approved indications
Cabometyx (cabozantinib tablets [7-11]	▪ Advanced RCC in patients who have received prior anti-angiogenic therapy (April 2016). ▪ Advanced RCC in the first line setting (December 2017). ▪ HCC in patients who have been previously treated with sorafenib (January 2019).
Cometriq (cabozantinib capsules) [12]	▪ MTC (November 2012).
HCC – Hepatocellular carcinoma; **MTC** – Metastatic thyroid cancer; **RCC** – Renal cell carcinoma.	

4. CABOZANTINIB DOSING/ ADMINISTRATION

Table 2. Cabozantinib dosing and administration

	Cabometyx	Cometriq
Dosage form	It is available as 20mg, 40mg and 60mg tablets.	It is available as 20mg and 80mg capsules.
Dosing		
RCC & HCC	60mg orally once daily to be continued until disease progression or unacceptable toxicity occurs.	
MTC		140mg orally once daily to be continued until disease progression or unacceptable toxicity occurs.
Administration [13,14]	▪ Instruct patients not to eat for at least 2 hours before and at least 1 hour after cabozantinib. ▪ Cabometyx and cometriq are not interchangeable	
HCC – Hepatocellular carcinoma; **MTC** – Metastatic thyroid cancer; **RCC** – Renal cell carcinoma.		

5. CABOZANTINIB PHARMACOKINETICS

Table 3. Cabozantinib pharmacokinetics

	Cabometyx	Cometriq
Pharmacokinetics [14,15]		
Protein binding	≥ 99.7% to plasma protein	
Metabolism	Hepatic via CYP3A4	
Absorption (peak plasma concentration)	3-4 hours Steady state achieved on day 15	2-5 hours Steady state achieved on day 15
Bioavailability	A 19% increase in the peak plasma concentration of the tablet formulation (cabometyx) compared to the capsule formulation (cometriq), although the difference in AUC was < 10%.	
Elimination		
Half life	99 hours	55 hours
Clearance	2.2 L/hour	4.4 L/hour
Excretion	Feces (54%, 43% as unchanged drug), urine (27%)	

Pharmacokinetics (PK) is a relevant and obvious biomarker that could be used to optimize treatment through therapeutic drug monitoring (TDM). The purpose of this discussion is to integrate the available PK data about cabozantinib tablets and capsules into practical recommendations for personalization of treatment.

A pharmacokinetics study of cabozantinib tablets and capsules formulations has been conducted by Nguyen and colleagues [8]. Results revealed that plasma exposure values were similar (<10% difference) for both formulations and the 90% confidence intervals (CIs) around the ratio of geometric least square means (GLSM) were within the accepted bioequivalence limits of 80-125%. However, the GLSM for Cmax was 19% higher for the tablet formulation and the upper 90% CI for the ratio of GLSM (131.65%) was beyond the 80-125% range. This finding indicates that tablets and capsules formulations failed to fulfill the bioequivalence study acceptance criteria and should not be used interchangeably [14].

Another pharmacokinetics analysis indicated similar steady-state exposures (Ctrough,ss) at different doses among patients with metastatic thyroid cancer (MTC) (140 mg capsule), renal cell carcinoma (RCC) (60 mg tablet). The apparent oral clearance estimated by patients' pharmacokinetics model was 4.4 L/hour in MTC and 2.2 L/hour in RCC. These were unexpected results as Cmax and AUC of the tablet formulation (Cabometyx) and the capsule formulation (Cometriq) were similar following a single 140-mg dose [15, 16].

6. CABOMETYX AND COMETRIQ, ARE THEY INTERCHANGEABLE

Cabometyx (cabozantinib) tablets and cometriq (cabozantinib) capsules are not bioequivalent and should not be used interchangeably. If a patient must switch from cabozantinib capsules to cabozantinib tablets, the patient should continue at a cabometyx dose not to exceed 60mg or the current cometriq dose (whichever is lower). Do NOT substitute cabometyx tablets with cometriq capsules [17, 18].

7. CONCLUSION AND RECOMMENDATIONS

It is important to have postmarketing evaluation for the potential factors impacting pharmacokinetics of cabozantinib, such as patient population, formulations and doses in an integrated population pharmacokinetics model.

Each institution should have a generic prescribing policy. This policy must include drugs that cannot be prescribed generically. Cabozantinib should not be prescribed generically. It must be prescribed as cabometyx tablets or cometriq capsules as indicated.

Based on posology, cabometyx and cometriq should not be used interchangeably. In case a patient must switch from cabozantinib capsules to cabozantinib tablets, the patient should continue with cabometyxat a dose not exceeding 60mg or continue with the current cometriq dose, whichever is lower. Do NOT substitute cabometyx tablets with cometriq capsules.

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