CABOMETYX®
(cabozantinib) tablets

Treatment Management Guide

Strategies to manage adverse reactions and find the right dose as needed

FIRST- AND SECOND-LINE aRCC

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

SECOND-LINE HCC

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

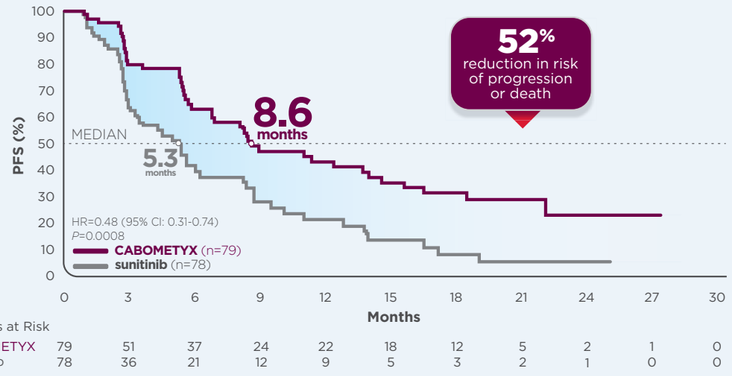
Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

The only TKI with superior efficacy in both 1L and 2L aRCC[1]

1L CABOSUN TRIAL — CABOMETYX is the only TKI with superior efficacy to sunitinib[1]*

PRIMARY ENDPOINT IN CABOSUN: PFS[1,2†]



CABOSUN was a randomized (1:1), open-label, multicenter, phase 2 trial of CABOMETYX vs sunitinib in 157 first-line patients with aRCC who had ≥1 IMDC risk factors.[1,2]

SECONDARY ENDPOINT IN CABOSUN

OS[1,2]

20% reduction in risk of death

HR=0.80 (95% CI: 0.53-1.21)

SECONDARY ENDPOINT IN CABOSUN

ORR[1,2]

20% CABOMETYX (n=79) **VS** **9%** sunitinib (n=78)

(95% CI: 12.0%-30.8%) (95% CI: 3.7%-17.6%)

- ORR was assessed by a retrospective blinded IRRC, and all responses were partial responses[1]
- The trial did not have a prespecified hypothesis for OS and ORR, and statistical testing of these endpoints was not performed[2]

***Patients had ≥1 IMDC risk factors.[1]**
†PFS was assessed by a retrospective blinded IRRC.[1]
‡After at least one prior anti-angiogenic therapy.[1]
§In the METEOR trial, the primary PFS analysis was conducted in the first 375 subjects randomized to treatment.[1]
‖PFS was confirmed by blinded IRRC.[1]
¶ORR was assessed by blinded IRRC using RECIST v1.1.[3]

1L=first-line; 2L=second-line; CI=confidence interval; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IRRC=independent radiology review committee; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; TKI=tyrosine kinase inhibitor.

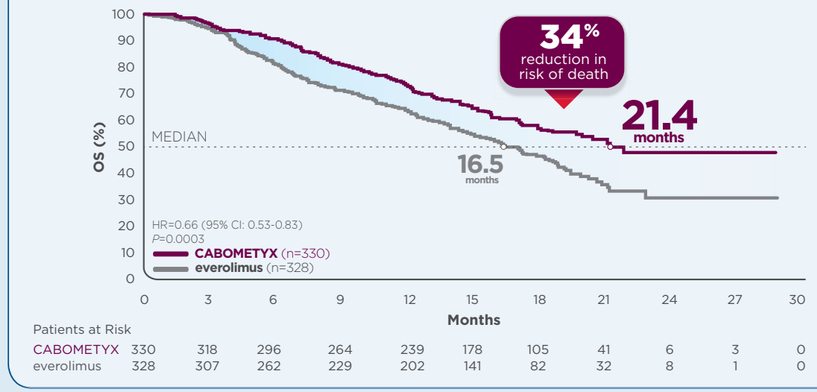
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Perforations and Fistulas: Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

2L METEOR TRIAL — CABOMETYX is the only TKI with superior OS, PFS, and ORR in 2L aRCC[1‡]

SECONDARY ENDPOINT IN METEOR: OS



METEOR was a randomized (1:1), open-label, phase 3 trial of CABOMETYX vs everolimus in 658 patients with aRCC who had previously received at least 1 prior anti-angiogenic treatment.[1,3]

PRIMARY ENDPOINT IN METEOR

MEDIAN PFS[1§‖]

7.4 months CABOMETYX (n=187) **VS** **3.8** months everolimus (n=188)

HR=0.58 (95% CI: 0.45-0.74); *P*<0.0001

SECONDARY ENDPOINT IN METEOR

ORR[1¶]

17% CABOMETYX (n=330) **VS** **3%** everolimus (n=328)

(95% CI: 13.0%-22.0%) (95% CI: 2.0%-6.0%)

(*P*<0.0001); partial responses only

National Comprehensive Cancer Network® (NCCN®)

NCCN PREFERRED — Cabozantinib (CABOMETYX) is **THE ONLY NCCN "PREFERRED" SINGLE-AGENT TKI OPTION** for 1L intermediate/poor risk and 2L clear cell aRCC[4]

The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Overall survival results

Superior OS in the treatment of 2L HCC[1]

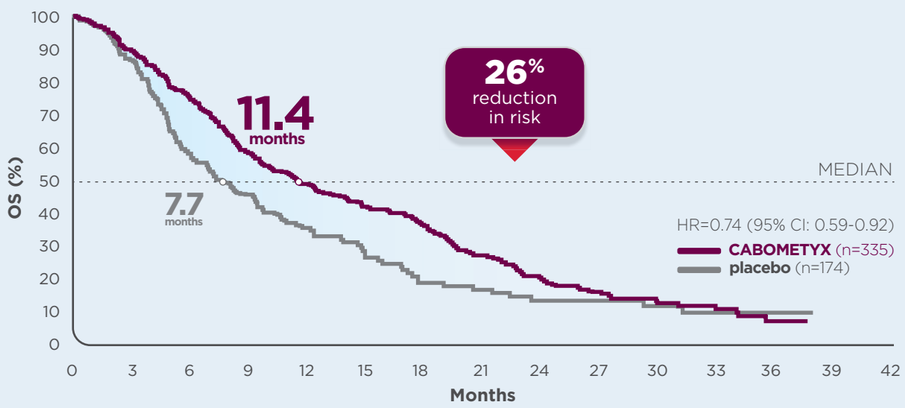
PRIMARY ENDPOINT: OS (ITT)

- Median OS was 10.2 months with CABOMETYX (n=470) vs 8.0 months with placebo (n=237) in patients who received at least one prior therapy (HR=0.76; 95% CI: 0.63-0.92; *P*=0.0049)

In a prespecified exploratory subgroup analysis of patients who received only 1 prior systemic therapy

CABOMETYX exceeded 11 months median OS in the second line[5,6]

SUBGROUP ANALYSIS: OS (SECOND LINE)[7*]



*No statistical procedure was employed for controlling type I error. Results should be considered hypothesis generating.[5]

CELESTIAL was a randomized (2:1), double-blind, phase 3 trial of CABOMETYX vs placebo in 707 post-sorafenib treated patients with Child-Pugh A HCC who had progressed on at least 1 prior systemic therapy.[1,5]

ITT=intent to treat.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Progression-free survival results

Superior PFS in the treatment of 2L HCC[1]

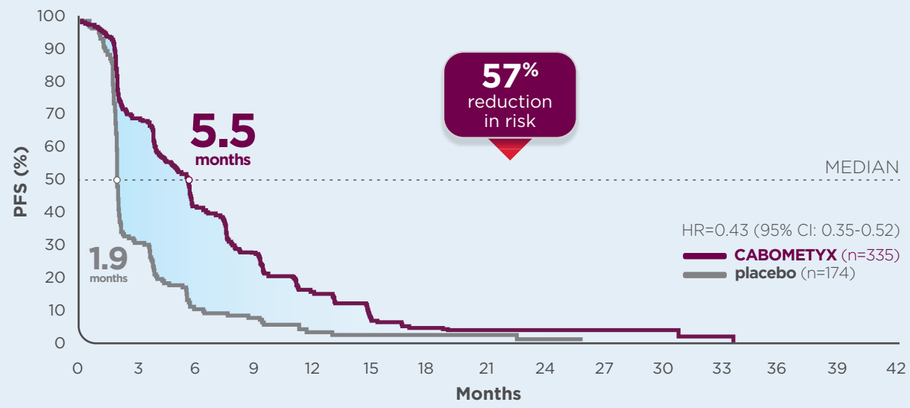
SECONDARY ENDPOINT: PFS (ITT)

- Median PFS was 5.2 months with CABOMETYX (n=470) vs 1.9 months with placebo (n=237) in patients who received at least one prior therapy (HR=0.44; 95% CI: 0.36-0.52; *P*<0.0001)

In a prespecified exploratory subgroup analysis of patients who received only 1 prior systemic therapy

CABOMETYX exceeded 5 months median PFS in the second line[5,6]

SUBGROUP ANALYSIS: PFS (SECOND LINE)[7†]



†No statistical procedure was employed for controlling type I error. Results should be considered hypothesis generating.[5]

National Comprehensive Cancer Network® (NCCN®)

NCCN CATEGORY 1

Following disease progression on first-line systemic treatment

Cabozantinib (CABOMETYX) is **RECOMMENDED AS A CATEGORY 1, SUBSEQUENT-LINE TREATMENT OPTION FOR HCC** (Child-Pugh A)[8‡]

‡Data reflect use after sorafenib. Lenvatinib is recommended by the NCCN as a first-line systemic therapy option, but there are no data to define optimal treatment for those who progress on lenvatinib.[8]

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Available in 3 strengths to help you find the right dose for your patients when needed[1]

Recommended starting dose	60 mg daily
First reduction	40 mg daily
Second reduction	20 mg daily

Tablets shown are not actual size.

- Do not substitute CABOMETYX tablets with cabozantinib capsules

For important dosing and administration information about food interactions, drug-drug interactions, patients undergoing surgery, and patients with hepatic impairment, please see the **full Prescribing Information**.

Recommended dose of CABOMETYX for patients with hepatic impairment[1]

Child-Pugh B: Reduce the starting dose of CABOMETYX to **40 mg once daily** in patients with moderate hepatic impairment

- Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C)

Pharmacokinetics[1]

- The predicted terminal half-life is approximately 99 hours

You may need to adjust the CABOMETYX dose based on individual patient safety and tolerability[1]

If ARs occur, consider supportive care and/or adjust the dose

FOR INTOLERABLE GRADE 2 ARs, OR GRADE 3-4 ARs

Withhold
CABOMETYX

Wait
until improvement or resolution (return to baseline or resolution to Grade 1)

Restart
For patients who previously received 60 mg or 40 mg: RESTART CABOMETYX at a dose reduced by 20 mg

Resume
For patients who previously received 20 mg: RESUME CABOMETYX at 20 mg if tolerated; otherwise, DISCONTINUE

- ONJ occurred in <1% of patients treated with CABOMETYX. Withhold CABOMETYX for development of ONJ until complete resolution
- Permanently discontinue CABOMETYX for severe hemorrhage, development of a GI perforation or Grade 4 fistula, acute myocardial infarction or arterial/venous thromboembolic events that require medical intervention, severe hypertension that cannot be controlled with anti-hypertensive therapy, hypertensive crisis, nephrotic syndrome, or reversible posterior leukoencephalopathy syndrome

AR=adverse reaction; GI=gastrointestinal; ONJ=osteonecrosis of the jaw.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Select adverse reactions across phase 3 CABOMETYX trials in aRCC and HCC*

METEOR trial in 2L aRCC

The most common reasons for dose reductions were diarrhea, PPE/HFS, fatigue, and hypertension[1]

CABOMETYX PATIENT EXPERIENCE FROM THE METEOR TRIAL (n=331)

	Diarrhea	PPE/HFS	Fatigue	Hypertension
All-grade incidence (Grade 3-4 incidence)[1]	74% (11%)	42% (8%)	56% (9%)	39% (16%)
Median time to first occurrence[7]	5 weeks	3.4 weeks	NA	3 weeks
Dose interruptions[7†]	22%	14%	12%	5%
Dose reductions[7†]	16%	11%	10%	7.6%
Discontinuations[7†]	<1%	<1%	1.2%	0%

NA=not available.
*Select ARs include those that may be managed with dose adjustments or supportive care strategies.[1]
†Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to these specific ARs.

No Grade 4 diarrhea, PPE/HFS, fatigue, or hypertension was reported in the METEOR trial[7]

Safety results from the CABOSUN trial are not included due to differences in data collection and smaller sample sizes.

CELESTIAL trial in 2L HCC

The most common reasons for dose reductions were diarrhea, PPE/HFS, fatigue, hypertension, and increased AST[1]

CABOMETYX PATIENT EXPERIENCE FROM THE CELESTIAL TRIAL (n=467)

	Diarrhea	PPE/HFS	Fatigue	Hypertension	Increased AST
All-grade incidence (Grade 3-4 incidence)[1]	54% (10%)	46% (17%)	45% (10%)	30% (16%)	73% (24%)
Median time to first occurrence[7]	4.1 weeks	3.1 weeks	NA	2.1 weeks	NA
Dose interruptions[7†]	15%	25%	13%	6.6%	9.4%
Dose reductions[7†]	10%	22%	7.5%	7.5%	5.6%
Discontinuations[7†]	1.1%	2.4%	1.5%	0.9%	0.9%

Grade 4 diarrhea, PPE/HFS, fatigue, and hypertension were reported in ≤1% of patients in the CELESTIAL trial[7]

The ARs included in this guide do not represent all of the possible side effects of CABOMETYX, and not all ARs may be manageable. Pages 6-10 of this PDF focus on ARs seen in the METEOR and CELESTIAL trials that most frequently led to dose reductions for patients receiving CABOMETYX therapy.

For additional safety information for the METEOR and CELESTIAL clinical trials, please see pages 11-12 of this PDF.

For information on how to counsel patients with other potential ARs, please see the Patient Counseling section of the **Prescribing Information**.

AST=aspartate aminotransferase; HFS=hand-foot syndrome; PPE=palmar-plantar erythrodysesthesia.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Diarrhea

In the CABOMETYX arm of the METEOR (n=331) and CELESTIAL (n=467) trials[1]

	aRCC	HCC
All-grade incidence (Grade 3-4 incidence)[1]	74% (11%)	54% (10%)
Median time to first occurrence[7]	5 weeks	4.1 weeks
Dose interruptions[7]*	22%	15%
Dose reductions[7]*	16%	10%
Discontinuations[7]*	<1%	1.1%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to these specific ARs.

CTCAE v4.03 grading identification: Diarrhea[9]

Grade 1	Increase of <4 stools per day over baseline
Grade 2	Increase of 4-6 stools per day over baseline
Grade 3	Increase of ≥7 stools per day over baseline Incontinence Hospitalization indicated Limiting self-care ADL†
Grade 4	Life-threatening consequences Urgent intervention indicated
Grade 5	Death

†Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.[9]

Withhold[1]

CABOMETYX in patients who develop intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea until return to baseline or improvement to Grade 1

Resume[1]

CABOMETYX at a reduced dose by 20 mg

If previously receiving 20-mg daily dose, resume at 20 mg if tolerated; otherwise, discontinue CABOMETYX

Management tips for diarrhea[10]

- Administer an antidiarrheal or antimotility agent at the first sign of diarrhea (more than 1 agent may be necessary)
- Implement supportive measures
  - Continuous oral hydration
  - Correction of fluid and electrolyte abnormalities
  - Small, frequent meals
  - Avoid lactose-containing products, high-fat meals, and alcohol

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Palmar-plantar erythrodysesthesia/ Hand-foot syndrome (PPE/HFS)

In the CABOMETYX arm of the METEOR (n=331) and CELESTIAL (n=467) trials[1]

	aRCC	HCC
All-grade incidence (Grade 3-4 incidence)[1]	42% (8%)	46% (17%)
Median time to first occurrence[7]	3.4 weeks	3.1 weeks
Dose interruptions[7]*	14%	25%
Dose reductions[7]*	11%	22%
Discontinuations[7]*	<1%	2.4%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to these specific ARs.

CTCAE v4.03 grading identification: PPE/HFS[9]

Grade 1	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain
Grade 2	Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain Limiting instrumental ADL†
Grade 3	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain Limiting self-care ADL‡

†Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.[9]
‡Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.[9]

Withhold[1]
CABOMETYX for intolerable Grade 2 or Grade 3 PPE until improvement to Grade 1

No modification[1]
for tolerable Grade 1 or 2

Resume[1]
CABOMETYX at a reduced dose by 20 mg

If previously receiving 20-mg daily dose, resume at 20 mg if tolerated; otherwise, discontinue CABOMETYX

Management tips for PPE/HFS[10]

Supportive care guidelines include:

- 20% urea cream twice daily and 0.05% clobetasol cream once daily
- Analgesics (NSAIDs/GABA agonists) for pain control if needed for Grade 2 or above

Early signs and manifestations of PPE/HFS include:

- Tingling
- Numbness
- Slight redness
- Mild hyperkeratosis
- Painful, symmetrical, red and swollen areas on palms and soles (lateral sides of fingers or periungual zones may also be affected)

All patients should be advised on prophylactic skin care, including:

- Use of hypoallergenic moisturizing creams
- Ointment for dry skin
- Sunscreen with sun protection factor (SPF) ≥30
- Avoidance of exposure of hands and feet to hot water
- Protection of pressure-sensitive areas of hands and feet
- Use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry
- Careful monitoring of patients with skin disorders for signs of infection (eg, abscess, cellulitis, or impetigo)

Adequate interventions are required to prevent worsening of skin symptoms, such as blisters, desquamations, ulcerations, or necrosis of affected areas.

Aggressive management of symptoms is recommended, including early referral to a dermatologist.

GABA=gamma-aminobutyric acid; NSAID=nonsteroidal anti-inflammatory drug.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Fatigue

In the CABOMETYX arm of the METEOR (n=331) and CELESTIAL (n=467) trials[1]

	aRCC	HCC
All-grade incidence (Grade 3-4 incidence)[1]	56% (9%)	45% (10%)
Median time to first occurrence[7]	NA	NA
Dose interruptions[7]*	12%	13%
Dose reductions[7]*	10%	7.5%
Discontinuations[7]*	1.2%	1.5%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to these specific ARs.

Withhold[1]

CABOMETYX for intolerable Grade 2 fatigue, and for Grade 3 or 4 fatigue

Resume[1]

CABOMETYX upon resolution/improvement (ie, return to baseline or resolution to Grade 1), resume at a reduced dose

If previously receiving 20-mg daily dose, resume at 20 mg if tolerated; otherwise, discontinue CABOMETYX

CTCAE v4.03 grading identification: Fatigue[9]

Grade 1	Fatigue relieved by rest
Grade 2	Fatigue not relieved by rest Limiting instrumental ADL†
Grade 3	Fatigue not relieved by rest Limiting self-care ADL‡

†Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.[9]
‡Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.[9]

Management tips for fatigue[10]

- Rule out common causes of fatigue, such as anemia, deconditioning, emotional distress, nutrition, sleep disturbance, and hypothyroidism
- Consider pharmacological management with psychostimulants, such as methylphenidate, after disease-specific morbidities have been excluded
- Dose interruption may be considered for Grade ≥3 fatigue despite optimal management, at the HCP's discretion

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Hypertension*

In the CABOMETYX arm of the METEOR (n=331) and CELESTIAL (n=467) trials[1]

	aRCC	HCC
All-grade incidence (Grade 3-4 incidence)[1]	39% (16%)	30% (16%)
Median time to first occurrence[7]	3 weeks	2.1 weeks
Dose interruptions[7†]	5%	6.6%
Dose reductions[7†]	7.6%	7.5%
Discontinuations[7†]	0%	0.9%

*Grouped term. Includes hypertension, blood pressure increased, hypertensive crisis, and blood pressure fluctuation.
†Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to these specific ARs.

CTCAE v4.03 grading identification: Hypertension[9]

Grade 1	Pre-hypertension (SBP 120-139 mm Hg or DBP 80-89 mm Hg)
Grade 2	Stage 1 hypertension (SBP 140-159 mm Hg or DBP 90-99 mm Hg) Recurrent or persistent (≥24 hours) Symptomatic increase by >20 mm Hg (DBP) or to >140/90 mm Hg if previously within normal limits Medical intervention indicated Anti-hypertensive monotherapy indicated
Grade 3	Stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) More than 1 drug or more intensive therapy than previously used may be indicated Medical intervention indicated
Grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurological deficit, hypertensive crisis) Urgent intervention indicated
Grade 5	Death

Withhold[1]
CABOMETYX for hypertension that is not adequately controlled with medical management

Resume[1]
When controlled, resume CABOMETYX at a reduced dose

If previously receiving 20-mg daily dose, resume at 20 mg if tolerated; otherwise, discontinue CABOMETYX

Discontinue[1]
CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis

Management tips for hypertension[10]

- Monitor and optimize BP before initiation and regularly during CABOMETYX treatment
- Other than for hypertension requiring immediate therapy, confirm the presence of new or worsened hypertension at a second visit (within 1 week) before taking therapeutic action

For SBP >150 mm Hg but <160 mm Hg or DBP >100 mm Hg but <110 mm Hg‡:

- Optimize anti-hypertensive treatment by adding new or additional anti-hypertensive medications and/or increasing dose of existing medications
- Reduce CABOMETYX treatment by 1 dose level if optimized anti-hypertensive therapy (usually to include 3 agents) does not result in SBP <150 mm Hg or DBP <100 mm Hg
- If patient is symptomatic, interrupt treatment

Hypertensive crisis or hypertensive encephalopathy:

- Discontinue CABOMETYX treatment

‡Or a lower threshold, based on clinical judgment.
BP=blood pressure; DBP=diastolic blood pressure; mm Hg=millimeter of mercury; SBP=systolic blood pressure.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Increased aspartate aminotransferase (AST)

In the CABOMETYX arm of the CELESTIAL (n=467) trial[1]

	HCC
All-grade incidence (Grade 3-4 incidence)[1]	73% (24%)
Median time to first occurrence[7]	NA
Dose interruptions[7]*	9.4%
Dose reductions[7]*	5.6%
Discontinuations[7]*	0.9%

*Percentages represent the number of dose interruptions, dose reductions, and discontinuations due to these specific ARs.

CTCAE v4.03 grading identification: Increased AST[9]

Grade 1	>ULN - 3.0 x ULN
Grade 2	>3.0 - 5.0 x ULN
Grade 3	>5.0 - 20.0 x ULN
Grade 4	>20.0 x ULN

Withhold[11]

CABOMETYX for Grade 2 elevated AST that cannot be adequately managed, or ≥ Grade 3 elevated AST if patients had an AST of ≤3 x ULN at baseline, or when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests

Resume[1,11]

If hepatic toxicity resolves, resume CABOMETYX at a reduced dose

If previously receiving 20-mg daily dose, resume at 20 mg if tolerated; otherwise, discontinue CABOMETYX

Discontinue[11]

Permanently discontinue CABOMETYX if hepatic dysfunction is not reversible, or if elevations >3 x ULN of ALT or AST concurrent with >2 x ULN total bilirubin without other explanation

Management tips for hepatobiliary disorders[11]

- More frequent monitoring of transaminases should be considered and treatment should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels
- If possible, hepatotoxic concomitant medications should be discontinued in cases of increased values of ALT, AST, or total bilirubin
- Evaluation of patients with elevated transaminases or total bilirubin should be individualized and guided by the presence of specific risk factors, such as illnesses that affect liver function, concomitant hepatotoxic medication, alcohol consumption, and cancer-related causes
- ARs that are based on hepatic dysfunction should be managed according to locally accepted clinical practice, including monitoring of appropriate laboratory functions

ALT=alanine aminotransferase; ULN=upper limit of normal.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX safety in the METEOR study

ARs occurring in ≥10% of patients in the CABOMETYX arm[1]

Percentage (%) of Patients

	CABOMETYX (n=331)*		everolimus (n=322)	
	All Grades†	Grade 3-4	All Grades†	Grade 3-4
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain‡	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
PPE	42	8	6	<1
Rash‡	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension‡	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

*One subject randomized to everolimus received CABOMETYX.
†National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0).
‡These ARs are grouped terms. For details, please see full Prescribing Information.

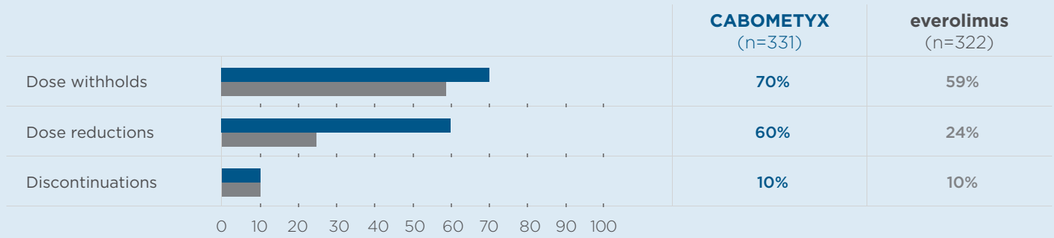
Laboratory abnormalities occurring in ≥25% of patients in the CABOMETYX arm[1]

Percentage (%) of Patients

	CABOMETYX (n=331)		everolimus (n=322)	
	All Grades†	Grade 3-4	All Grades†	Grade 3-4
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia§	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

§Based on laboratory abnormalities.[1]

Holding and reducing the dose can help to manage ARs with CABOMETYX[1]



- Dose adjustments were allowed in the METEOR trial, resulting in a mean average daily dose for CABOMETYX of 45 mg[7]

ALP=alkaline phosphatase; GGT=gamma-glutamyl transferase.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

CABOMETYX safety in the CELESTIAL study

ARs occurring at a higher incidence in patients treated with CABOMETYX (Between-arm difference of ≥5% [All Grades] or ≥2% [Grade 3-4])[1]

Percentage (%) of Patients

	CABOMETYX (n=467)		placebo (n=237)	
	All Grades*	Grade 3-4	All Grades*	Grade 3-4
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
PPE	46	17	5	0
Rash†	21	2	9	<1
Vascular				
Hypertension‡	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

*NCI-CTCAE v4.0.
†Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected.
‡Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased.

Laboratory abnormalities occurring at a higher incidence in patients treated with CABOMETYX (Between-arm difference of ≥5% [All Grades] or ≥2% [Grade 3-4])[1]

Percentage (%) of Patients

	CABOMETYX (n=467)		placebo (n=237)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

Holding and reducing the dose can help to manage ARs with CABOMETYX[1,5,7]

	CABOMETYX (n=467)	placebo (n=237)
Dose withholds	84%	37%
Dose reductions	62%	13%
Discontinuations	16%	3%

- Dose adjustments were allowed in the CELESTIAL trial, resulting in a mean average daily dose for CABOMETYX of 37 mg[7]

The overall efficacy results in the CABOMETYX trials were achieved in the context of dose modifications[1]

LDH=lactate dehydrogenase.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

INDICATIONS

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2020. **2.** Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): progression-free survival by independent review and overall survival update. *Eur J Cancer.* 2018;94:115-125. **3.** Choueiri TK, Escudier B, Powles T, 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(7):917-927. doi:10.1016/S1470-2045(16)30107-3. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.2.2020. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 9, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. **5.** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018;379:54-63. doi:10.1056/NEJMoa1717002. **6.** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018;379(1):54-63. doi:10.1056/NEJMoa1717002 [supplementary appendix]. **7.** Data on file. Exelixis, Inc. **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers V.3.2019. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 2, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. **9.** National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Published June 14, 2010. Accessed January 9, 2018. **10.** Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19):1814-1823. doi:10.1056/NEJMoa1510016 [study protocol]. **11.** Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018;379(1):54-63. doi:10.1056/NEJMoa1717002 [study protocol].

Please see full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Dose modifications can help you manage certain ARs and find the right CABOMETYX dose for your patients when needed[1]

- **Convenient**, once-daily oral dosing
- CABOMETYX is available in **3 strengths**
  - Recommended starting dose: 60 mg daily
  - Dose after first reduction: 40 mg daily
  - Dose after second reduction: 20 mg daily
- You may need to adjust the CABOMETYX dose based on individual patient safety and tolerability

Dose Exchange Program: Supporting your patients who require a dose modification during CABOMETYX treatment

- Patients who require a dose reduction will receive a free 15-tablet supply of CABOMETYX in the new lower dose. Additional restrictions and eligibility rules apply
- To obtain a Dose Exchange Program Form, **contact your sales representative**, call EASE at **1-844-900-EASE (3273)**, or visit www.EASE.us

This description of the Exelixis Access Services® (EASE) program, including the Dose Exchange program, is for informational purposes only. Exelixis® makes no representation or guarantee concerning reimbursement or coverage for any service or item. Information provided through the Exelixis Access Services program does not constitute medical or legal advice and is not intended to be a substitute for a consultation with a licensed health care provider, legal counsel, or applicable third-party payer(s). Exelixis reserves the right to modify the program at any time without notice.

SELECT IMPORTANT SAFETY INFORMATION

The full Prescribing Information for CABOMETYX includes Warnings and Precautions for: hemorrhage, perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, PPE, proteinuria, ONJ, impaired wound healing, RPLS, and embryo-fetal toxicity.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information.

CABOMETYX® (cabozantinib) tablets

Learn more at CABOMETYXhcp.com

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