



# Managing Patients With NEUROENDOCRINE TUMORS (NET) on CABOMETYX® (cabozantinib)

## Clinical Resource Guide

### INDICATIONS

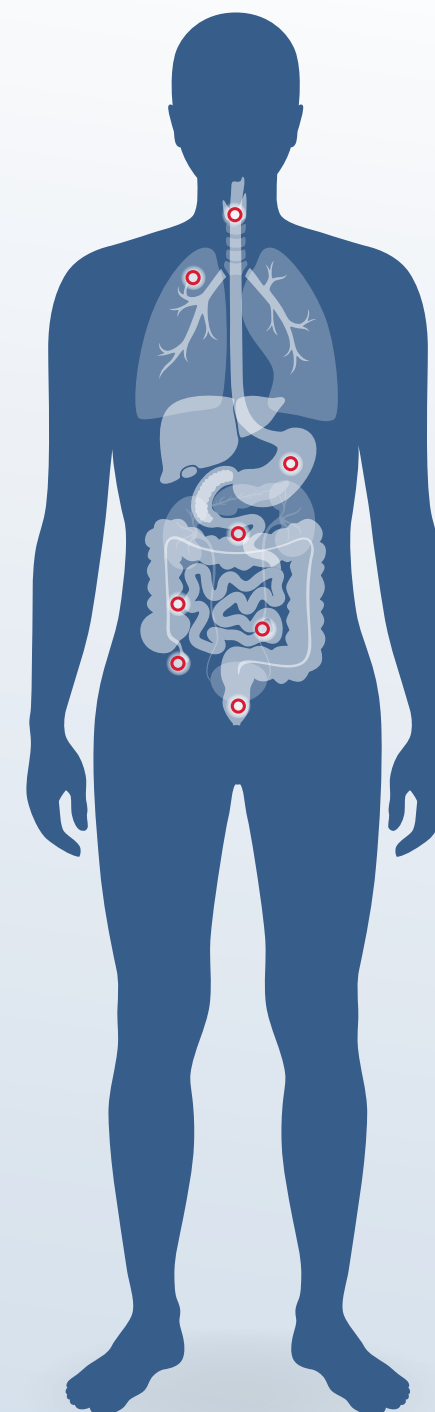
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET).

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extrapancreatic neuroendocrine tumors (epNET).

### IMPORTANT SAFETY INFORMATION

#### WARNINGS AND PRECAUTIONS

**Hemorrhage:** CABOMETYX can cause severe and fatal hemorrhages. The incidence of Grade 3-5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

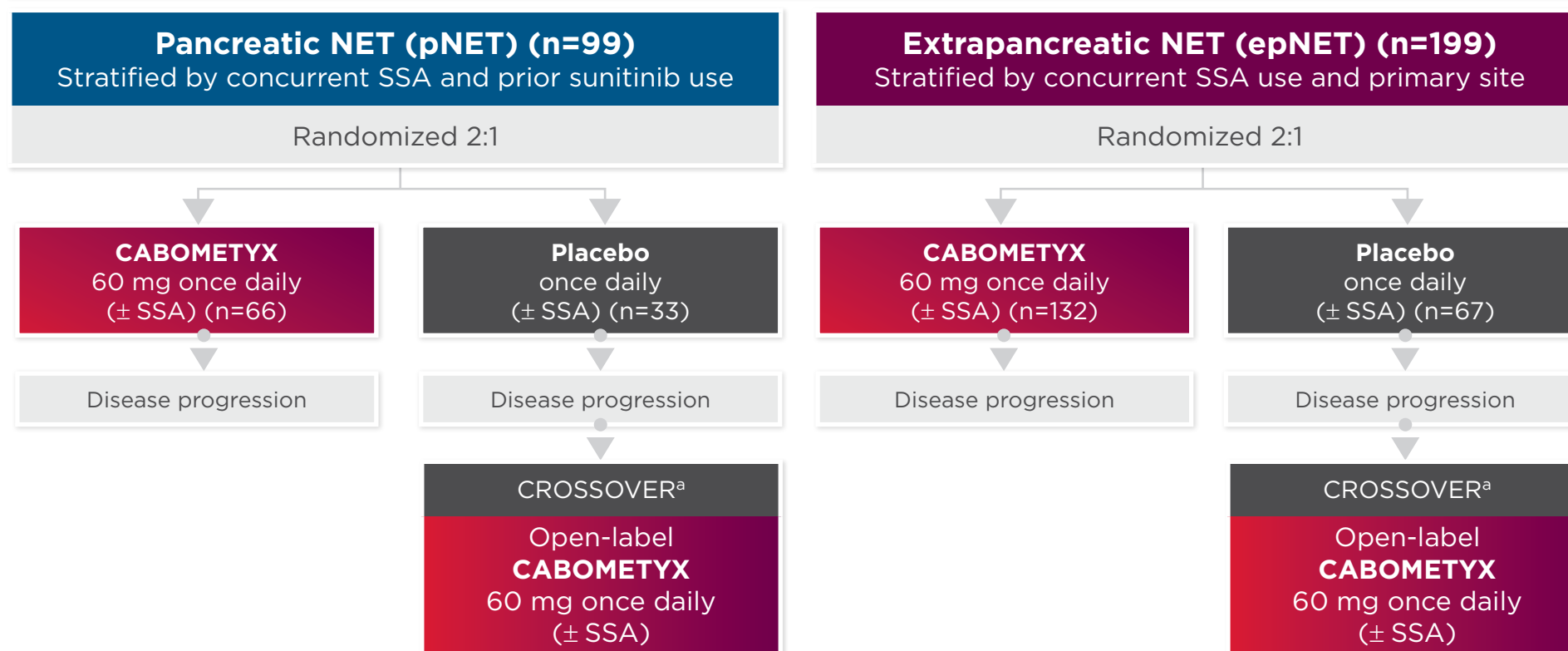


For the first time, a Phase 3 trial encompasses the wide-ranging heterogeneity of NET<sup>1-7</sup>

**CABINET: A randomized (2:1), double-blind, placebo-controlled, NCI-sponsored Phase 3 trial<sup>1,7</sup>**



**Patients with neuroendocrine tumors (NET) (N=298)<sup>1</sup>**



**Inclusion criteria<sup>7</sup>:**

- Progression or intolerance following ≥1 FDA-approved systemic therapy, not including SSAs
- Well- to moderately differentiated NET
- Functional and nonfunctional NET
- Tumor Grades 1-3
- ECOG PS 0-2
- Disease progression ≤12 months before randomization
- Concurrent SSA use permitted if a stable dose was received for ≥2 months

**CABINET allowed all sites of origin, including the lungs, GI tract, and pancreas<sup>7</sup>**

Prior FDA-approved systemic therapy included everolimus, Lu-177 dotatate, and sunitinib.<sup>7</sup>

▶ **Primary endpoint: PFS by BIRC<sup>1</sup>**

▶ **Secondary endpoints: ORR, OS, safety, and tolerability<sup>7,b</sup>**

<sup>a</sup>Unblinding and crossover to open-label CABOMETYX allowed after confirmation of progressive disease by real-time central radiology review.<sup>1</sup>

<sup>b</sup>As recommended by the Data and Safety Monitoring Board, the CABINET trial was unblinded before the final prespecified efficacy analysis, allowing all remaining placebo patients to cross over to CABOMETYX.<sup>7</sup>

CABINET was sponsored by the National Cancer Institute (NCI), a part of the National Institutes of Health, and initiated in 2018 by the NCI-funded National Clinical Trials Network group, the Alliance for Clinical Trials in Oncology (Alliance), to address the unmet needs in NET.<sup>7</sup>

Tumor assessments were done every 12 weeks by radiographic imaging for tumor response and progression (as determined by RECIST 1.1).<sup>7</sup>

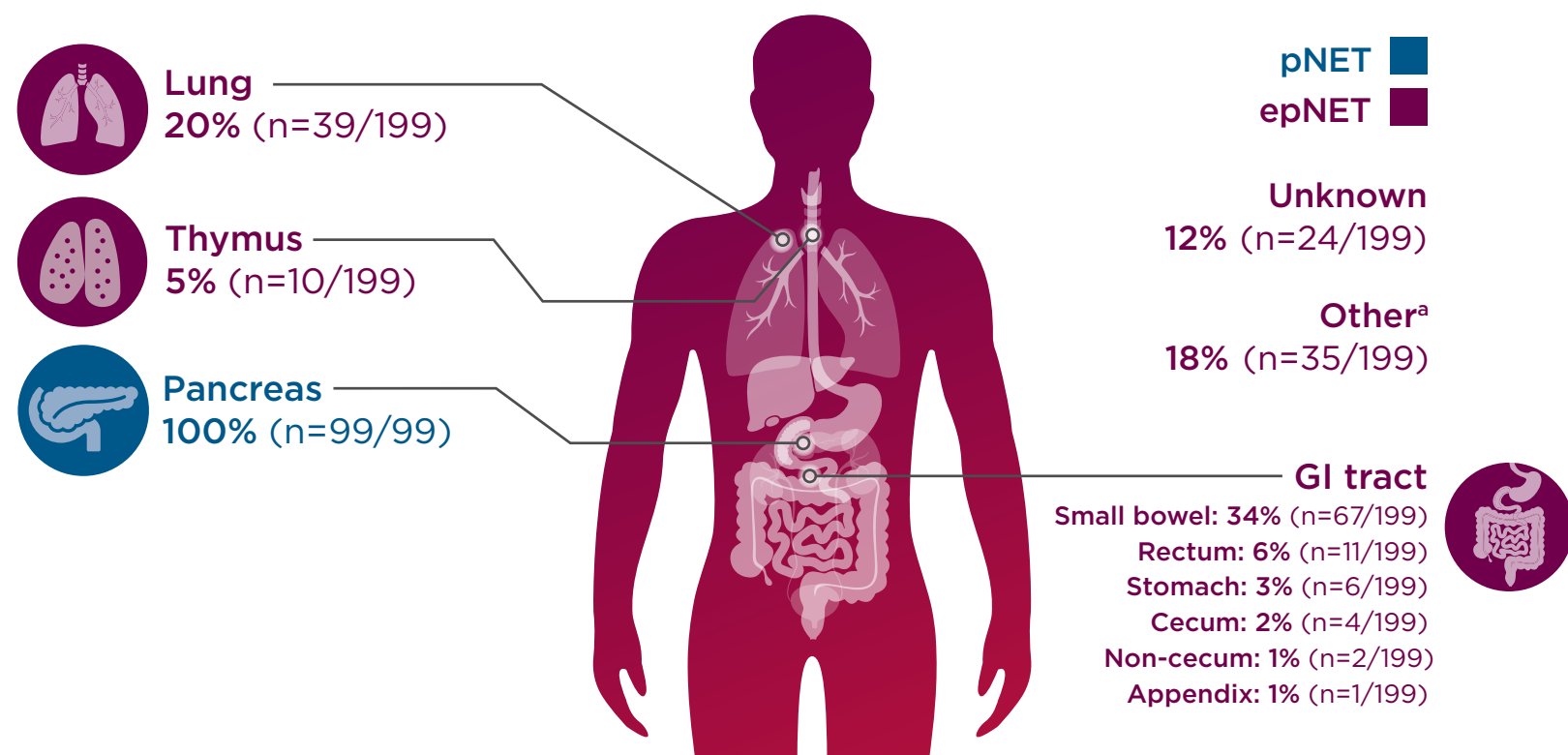
BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; GI, gastrointestinal; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SSA, somatostatin analogue.

**Please see additional Important Safety Information and full Prescribing Information.**

 **CABOMETYX<sup>®</sup>**  
(cabozantinib) tablets  
60 mg | 40 mg | 20 mg

# CABINET enrolled a broad patient population, allowing patients across all sites of origin<sup>7</sup>

## CABINET patients by site of origin<sup>8</sup>



## CABINET evaluated a range of patients<sup>7,8</sup>

- >70% with Grade 2-3 tumors
- Patients who received concurrent SSA
  - pNET: 58% with CABOMETYX vs 55% with placebo
  - epNET: 54% with CABOMETYX vs 63% with placebo
- Patients with functional disease
  - pNET: 18% with CABOMETYX vs 12% with placebo
  - epNET: 30% with CABOMETYX vs 39% with placebo

**CABINET was the first Phase 3 trial across pNET and epNET to include patients with prior peptide receptor radionuclide therapy (PRRT)<sup>3,6,9-11</sup>**

Percentages for the epNET cohort exceed 100 due to rounding.

<sup>a</sup>Other sites included small bowel, mesentery, ampulla, midgut, hindgut, biliary tract, larynx, presacral space, kidney, and ethmoid sinus.<sup>8</sup>

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(cabozantinib) tablets  
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CABOMETYX efficacy in NET



Primary endpoint: PFS<sup>1</sup>

| pNET   | QUADRUPLED MEDIAN PFS                            |  |
|--|--|--|
| 13.8 months<br>CABOMETYX<br>(95% CI, 8.9-17.0; n=66) | VS<br>HR, 0.22<br>(95% CI, 0.12-0.41)<br>P<.0001 | 3.3 months<br>Placebo<br>(95% CI, 2.8-5.7; n=33) |
| 78% reduction in risk of progression or death        |  |  |

epNET DOUBLED MEDIAN PFS

|  |  |  |
|--|--|--|
| 8.5 months<br>CABOMETYX<br>(95% CI, 6.8-12.5; n=132) | VS<br>HR, 0.40<br>(95% CI, 0.26-0.61)<br>P<.0001 | 4.2 months<br>Placebo<br>(95% CI, 3.0-5.7; n=67) |
| 60% reduction in risk of progression or death        |  |  |

Secondary endpoint: ORR<sup>1,7,8</sup>

Descriptive analyses

| ORR <sup>a</sup>              |    |                             |
|-------------------------------|----|-----------------------------|
| 18%<br>CABOMETYX<br>(n=12/66) | VS | 0%<br>Placebo               |
| SD <sup>b</sup>               |    |                             |
| 62%<br>CABOMETYX<br>(n=41/66) | VS | 55%<br>Placebo<br>(n=18/33) |
| DCR <sup>c</sup>              |    |                             |
| 80%<br>CABOMETYX              | VS | 55%<br>Placebo              |

| ORR <sup>a</sup>               |    |                             |
|--------------------------------|----|-----------------------------|
| 5%<br>CABOMETYX<br>(n=7/132)   | VS | 0%<br>Placebo               |
| SD <sup>b</sup>                |    |                             |
| 64%<br>CABOMETYX<br>(n=85/132) | VS | 52%<br>Placebo<br>(n=35/67) |
| DCR <sup>c</sup>               |    |                             |
| 69%<br>CABOMETYX               | VS | 52%<br>Placebo              |

<sup>a</sup>All responses confirmed were partial responses.<sup>7</sup>

<sup>b</sup>Stable disease (SD) is defined as neither sufficient shrinkage to qualify as partial response nor sufficient increase to qualify as PD.<sup>12</sup> Stable disease may reflect the natural history of disease rather than any effect of the drug.<sup>13</sup>

<sup>c</sup>Disease control rate (DCR) is defined as the percentage of patients with a complete response, partial response, or stable disease, as measured by RECIST v1.1.<sup>8</sup>

HR, hazard ratio; PD, progressive disease.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

**Perforations and Fistulas:** Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

Please see additional Important Safety Information and full Prescribing Information.



## Updated analysis

### OS results from CABINET<sup>1</sup>

OS data were not mature at the time of the updated analysis and may be impacted by crossover

**pNET****Updated OS**

**48%** Deaths **CABOMETYX** (n=66) **VS** **52%** Deaths **Placebo** (n=33) | (HR, 1.01; 95% CI, 0.55-1.83)

**52% of placebo arm patients crossed over to open-label CABOMETYX.**

**epNET****Updated OS**

**63%** Deaths **CABOMETYX** (n=132) **VS** **60%** Deaths **Placebo** (n=67) | (HR, 1.05; 95% CI, 0.71-1.54)

**37% of placebo arm patients crossed over to open-label CABOMETYX.**

The CABINET trial was unblinded early, and patients were allowed to cross over to open-label CABOMETYX regardless of whether they had experienced progression. A later updated OS analysis was conducted when 49 deaths were observed in the pNET cohort and 123 deaths observed in the epNET cohort.

#### IMPORTANT SAFETY INFORMATION (cont'd)

##### WARNINGS AND PRECAUTIONS

**Thrombotic Events:** CABOMETYX can cause arterial or venous thromboembolic event. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

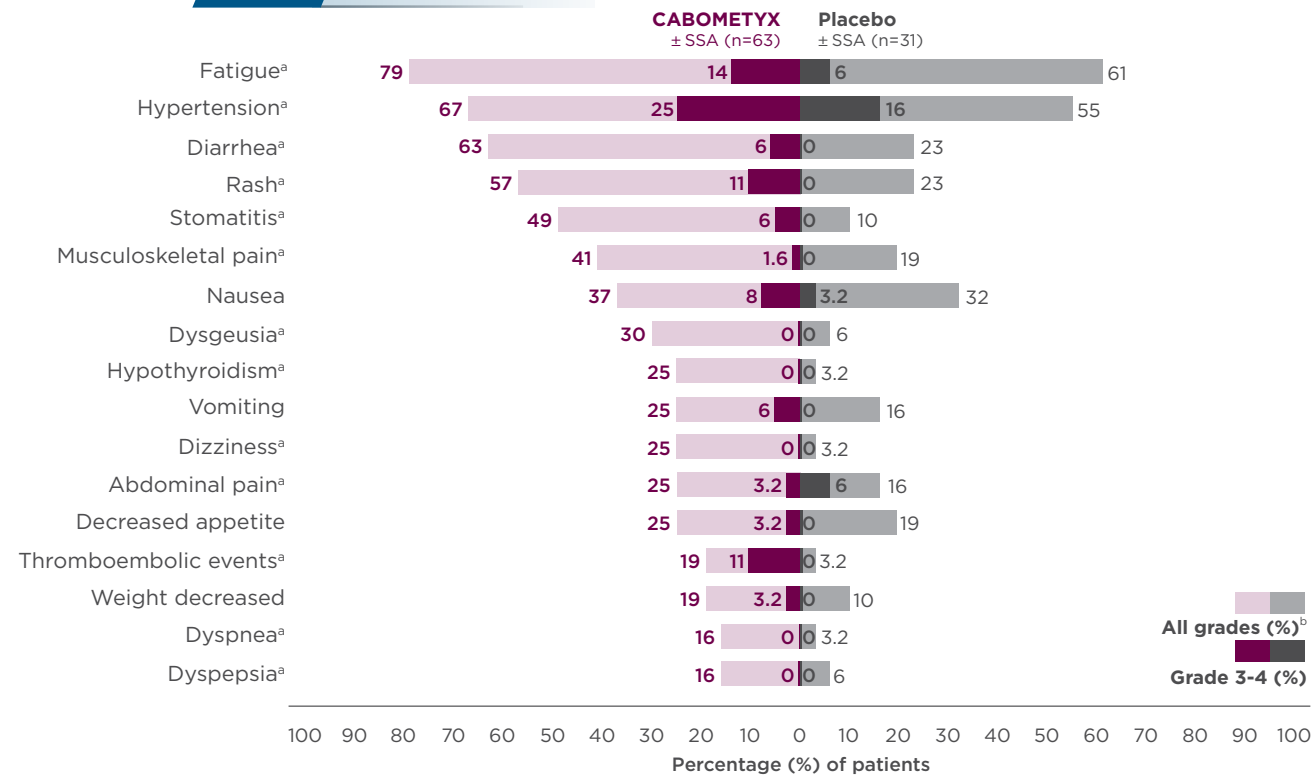
**Please see additional Important Safety Information and full Prescribing Information.**



# The safety profile observed in CABINET was consistent with the known CABOMETYX safety profile<sup>7</sup>

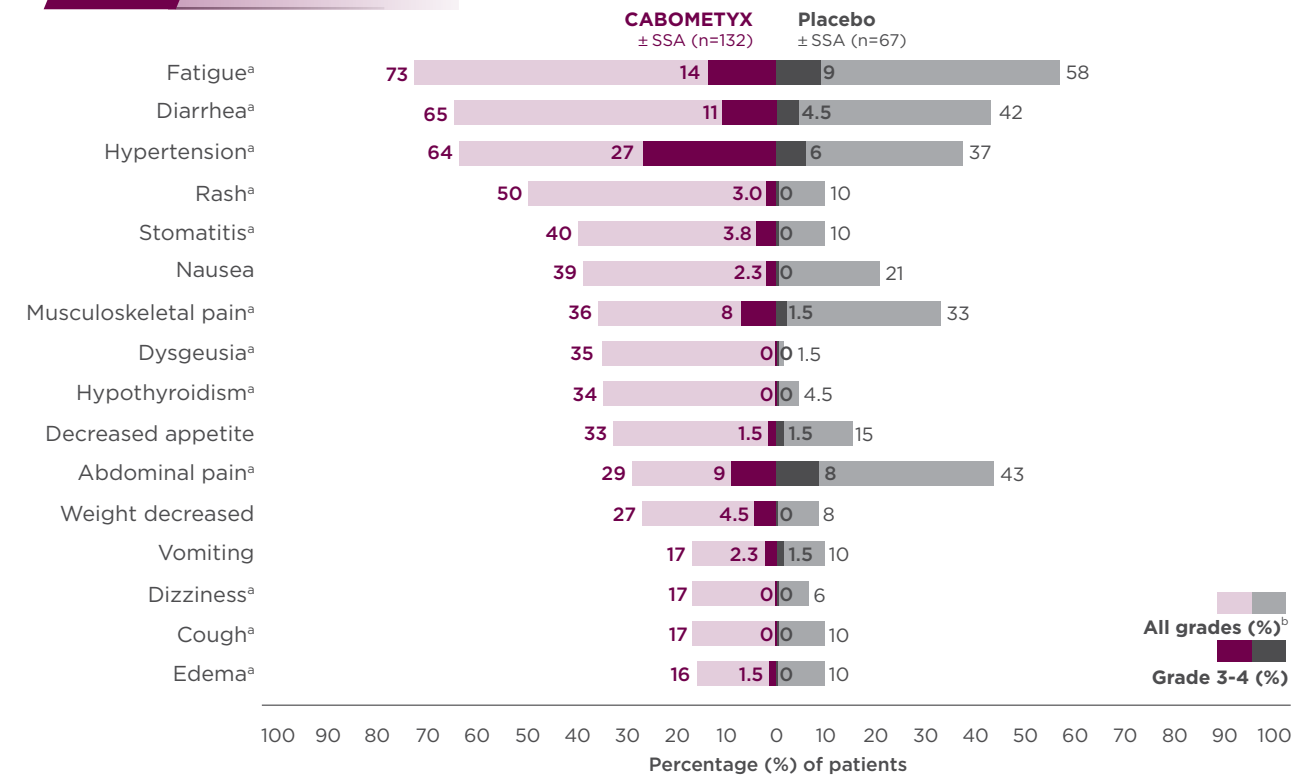


## pNET Adverse reactions occurring in ≥15% of CABOMETYX patients<sup>1,7</sup>



Clinically relevant ARs in <15% of patients who received CABOMETYX included peripheral neuropathy, hemorrhage, cardiac arrhythmia, hypotension, alopecia, and hair color changes.<sup>1</sup>

## epNET Adverse reactions occurring in ≥15% of CABOMETYX patients<sup>1,7</sup>



Clinically relevant ARs in <15% of patients who received CABOMETYX included cardiac arrhythmia, hemorrhage, thromboembolic events, kidney injury, proteinuria, hypotension, peripheral neuropathy, reversible posterior leukoencephalopathy syndrome, alopecia, and hair color changes.<sup>1</sup>

CABINET included patients with functional disease<sup>1</sup>

<sup>a</sup>These ARs are grouped terms. For details, please see full Prescribing Information.<sup>1</sup>

<sup>b</sup>NCI CTCAE v5.0.<sup>1</sup>

AR, adverse reaction; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Please see additional **Important Safety Information** and **full Prescribing Information**.



# No new safety signals were observed in the CABINET trial<sup>7</sup>



**pNET**      Laboratory abnormalities occurring in ≥10% of CABOMETYX patients<sup>1,7</sup>

|   | CABOMETYX ± SSA (n=63)      |               | Placebo ± SSA (n=31)        |               |
|---|-----------------------------|---------------|-----------------------------|---------------|
|   | All grades <sup>a</sup> (%) | Grade 3-4 (%) | All grades <sup>a</sup> (%) | Grade 3-4 (%) |
| <b>Chemistry</b>                              |                             |               |                             |               |
| Increased AST                                 | 76                          | 1.6           | 48                          | 0             |
| Increased ALT                                 | 75                          | 1.6           | 39                          | 3.2           |
| Hyperglycemia <sup>b</sup>                    | 37                          | 3.2           | 48                          | 3.2           |
| Hypophosphatemia <sup>b</sup>                 | 25                          | 0             | 6                           | 0             |
| Increased ALP <sup>b</sup>                    | 22                          | 3.2           | 23                          | 0             |
| Hypocalcemia <sup>b</sup>                     | 17                          | 0             | 3.2                         | 0             |
| Hyponatremia <sup>b</sup>                     | 16                          | 1.6           | 16                          | 0             |
| Blood bilirubin increased <sup>b</sup>        | 14                          | 4.8           | 6                           | 3.2           |
| Hyperkalemia                                  | 14                          | 1.6           | 10                          | 0             |
| Hypoalbuminemia <sup>b</sup>                  | 14                          | 0             | 10                          | 0             |
| Hypoglycemia <sup>b</sup>                     | 11                          | 0             | 6                           | 0             |
| Hypomagnesemia <sup>b</sup>                   | 11                          | 0             | 6                           | 0             |
| Hypokalemia                                   | 10                          | 1.6           | 3.2                         | 0             |
| <b>Hematology</b>                             |                             |               |                             |               |
| Platelet count decreased <sup>b</sup>         | 37                          | 0             | 19                          | 0             |
| Neutrophil count decreased <sup>b</sup>       | 27                          | 1.6           | 6                           | 0             |
| Hemoglobin decreased <sup>b</sup>             | 25                          | 1.6           | 32                          | 0             |
| Lymphocyte count decreased <sup>b</sup>       | 22                          | 8             | 16                          | 0             |
| White blood cell count decreased <sup>b</sup> | 19                          | 1.6           | 3.2                         | 0             |

**epNET**      Laboratory abnormalities occurring in ≥10% of CABOMETYX patients<sup>1,7</sup>

|   | CABOMETYX ± SSA (n=132)     |               | Placebo ± SSA (n=67)        |               |
|---|-----------------------------|---------------|-----------------------------|---------------|
|   | All grades <sup>a</sup> (%) | Grade 3-4 (%) | All grades <sup>a</sup> (%) | Grade 3-4 (%) |
| <b>Chemistry</b>                              |                             |               |                             |               |
| Increased AST                                 | 70                          | 3.8           | 21                          | 1.5           |
| Increased ALT                                 | 63                          | 0.8           | 18                          | 1.5           |
| Hyperglycemia <sup>b</sup>                    | 30                          | 0.8           | 39                          | 1.5           |
| Increased ALP <sup>b</sup>                    | 29                          | 4.5           | 30                          | 6             |
| Blood creatinine increased                    | 23                          | 0             | 12                          | 1.5           |
| Blood bilirubin increased <sup>b</sup>        | 20                          | 3.0           | 10                          | 6             |
| Hypoalbuminemia <sup>b</sup>                  | 20                          | 0.8           | 9                           | 0             |
| Hypocalcemia <sup>b</sup>                     | 20                          | 0             | 4.5                         | 0             |
| Hypokalemia <sup>b</sup>                      | 20                          | 2.3           | 10                          | 1.5           |
| Hypomagnesemia <sup>b</sup>                   | 20                          | 0.8           | 4.5                         | 0             |
| Hypophosphatemia <sup>b</sup>                 | 19                          | 0.8           | 4.5                         | 0             |
| Hyponatremia <sup>b</sup>                     | 16                          | 2.3           | 7                           | 1.5           |
| <b>Hematology</b>                             |                             |               |                             |               |
| Platelet count decreased <sup>b</sup>         | 55                          | 1.5           | 13                          | 1.5           |
| White blood cell count decreased <sup>b</sup> | 37                          | 3             | 4.5                         | 0             |
| Neutrophil count decreased <sup>b</sup>       | 36                          | 3             | 6                           | 0             |
| Hemoglobin decreased <sup>b</sup>             | 30                          | 2.3           | 19                          | 0             |
| Lymphocyte count decreased <sup>b</sup>       | 28                          | 9             | 18                          | 1.5           |

<sup>a</sup>These ARs are grouped terms. For details, please see full Prescribing Information.<sup>1</sup>  
<sup>b</sup>NCI CTCAE v5.0.<sup>1</sup>  
 ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Please see additional Important Safety Information and full Prescribing Information.**





The overall efficacy results in the CABINET trial were achieved in the context of dose modifications<sup>8</sup>



## pNET

## AR-related dose modification

## Dose holds

**83%** vs **42%**  
with CABOMETYX with placebo

## Dose reductions

**49%** vs **16%**  
with CABOMETYX with placebo

## Discontinuations

**19%** vs **10%**  
with CABOMETYX with placebo

## epNET

## AR-related dose modification

## Dose holds

**81%** vs **39%**  
with CABOMETYX with placebo

## Dose reductions

**38%** vs **6%**  
with CABOMETYX with placebo

## Discontinuations

**28%** vs **19%**  
with CABOMETYX with placebo

In the CABINET trial, the median average daily dose of CABOMETYX treatment was<sup>1</sup>

41 mg in pNET

43 mg in epNET



# CABOMETYX offers a once-daily starting dose<sup>1</sup>



**60 mg**  
once daily

Tablet shown is not  
actual size.

## Recommended starting dose for treatment of NET<sup>a-c</sup>

<sup>a</sup>For the treatment of adult and pediatric patients  $\geq 12$  years of age with previously treated, unresectable, locally advanced or metastatic, well-differentiated pNET or epNET.

<sup>b</sup>For adult and pediatric patients  $\geq 12$  years of age with bodyweight  $\geq 40$  kg.

<sup>c</sup>For pediatric patients  $\geq 12$  years of age with bodyweight  $< 40$  kg, start at **40 mg** once daily.

Treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity.



### Administer on an empty stomach

Administer CABOMETYX at least 1 hour before or at least 2 hours after eating



### Swallow CABOMETYX tablet whole

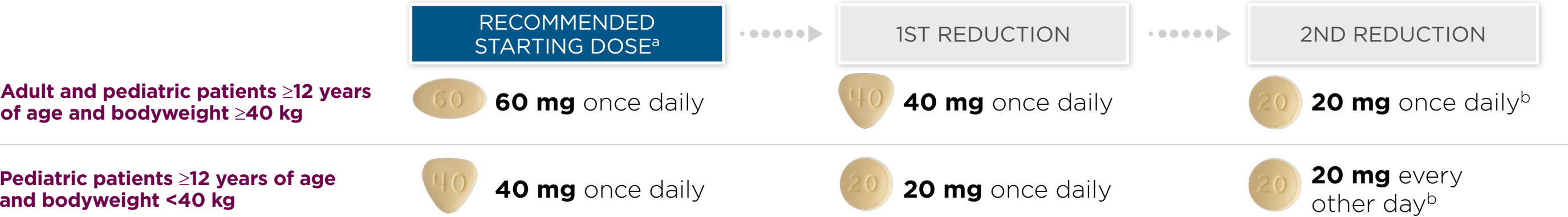
Do not crush, chew, or split CABOMETYX tablets

- Withhold CABOMETYX for at least 3 weeks prior to scheduled surgery, including dental surgery to reduce the risk of hemorrhage. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing
- Do not substitute CABOMETYX tablets with cabozantinib capsules
- Do not take a missed dose within 12 hours of the next dose
- Modify the dose for patients with moderate hepatic impairment and for patients taking drugs known to moderately or strongly induce CYP3A4 or strongly inhibit CYP3A4

**Pharmacokinetics:** The predicted terminal half-life is approximately 99 hours

# You may need to adjust the CABOMETYX dose based on individual patient safety and tolerability<sup>1</sup>


**CABOMETYX offers a once-daily starting dose and is available in 3 tablet strengths to help you find the right dose for your patients**



Tablets shown are not actual size.

**If ARs occur, consider supportive care and/or adjust the dose**  
**For intolerable Grade 2 ARs, Grade 3-4 ARs, and ONJ:**


- WITHHOLD** CABOMETYX
- WAIT** until improvement or resolution (return to baseline or resolution to Grade 1)
- RESTART** CABOMETYX at a dose reduced by 20 mg<sup>b</sup>



### Dose Exchange Program

Provides a free 15-tablet supply in the lower dose to help patients who require a dose reduction<sup>c,d</sup>

[www.ease.us/dose-exchange-form.pdf](http://www.ease.us/dose-exchange-form.pdf)




<sup>c</sup>Additional restrictions and eligibility rules apply.  
<sup>d</sup>Patients are required to return any unused product.

Permanently discontinue CABOMETYX for Grade 3 or 4 hemorrhage, development of a GI perforation or Grade 4 fistula, acute myocardial infarction or Grade 2 or higher cerebral infarction, Grade 3 or 4 arterial thromboembolic events or Grade 4 venous thromboembolic events, Grade 4 hypertension/hypertensive crisis or Grade 3 hypertension/hypertensive crisis that cannot be controlled, nephrotic syndrome, or reversible posterior leukoencephalopathy syndrome.

<sup>a</sup>Treatment with CABOMETYX should be continued until disease progression or unacceptable toxicity. <sup>b</sup>If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX. ONJ, osteonecrosis of the jaw.

**Please see additional Important Safety Information and full Prescribing Information.**


Diarrhea<sup>a</sup>



WITHHOLD<sup>1</sup>


CABOMETYX for Grade 2-4 diarrhea

Monitor and manage patients using antidiarrheals as indicated



WAIT<sup>1</sup>

Until improvement to ≤Grade 1



RESTART<sup>1</sup>

▼ CABOMETYX at a reduced dose; reduce by 20 mg daily

Adult and pediatric patients ≥12 years of age and bodyweight ≥40 kg

▼ Lowest dose is 20 mg daily

Pediatric patients ≥12 years of age and bodyweight <40 kg

▼ Lowest dose is 20 mg every other day

If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX

NCI-CTCAE v5.0 Grading Identification: **Diarrhea**<sup>14</sup>

| Grade | DESCRIPTION  |
|-------|--|
| 1     | <ul style="list-style-type: none"> <li>Increase of &lt;4 stools/day over baseline</li> </ul>   |
| 2     | <ul style="list-style-type: none"> <li>Increase of 4-6 stools/day over baseline</li> <li>Limiting instrumental ADL<sup>b</sup></li> </ul>                                |
| 3     | <ul style="list-style-type: none"> <li>Increase of ≥7 stools/day over baseline</li> <li>Hospitalization indicated</li> <li>Limiting self-care ADL<sup>c</sup></li> </ul> |
| 4     | <ul style="list-style-type: none"> <li>Life-threatening consequences</li> <li>Urgent intervention indicated</li> </ul>   |

Management tips for diarrhea

Advise patients to notify their health care provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements<sup>1</sup>

- Patients should also be instructed to contact their health care provider immediately for any of the following: diarrhea for more than 24 hours, inability to keep liquids down for more than 24 hours, blood in stool, fever<sup>15</sup>

Supportive measures for diarrhea<sup>16,17</sup>

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


<sup>a</sup>Median time to first occurrence of diarrhea was not available in CABINET.

<sup>b</sup>Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>c</sup>Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

ADL, activities of daily living.

Please see additional **Important Safety Information** and **full Prescribing Information**.



CABOMETYX<sup>®</sup>

(cabozantinib) tablets

60 mg | 40 mg | 20 mg

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



Median time to first occurrence of PPE was 4.3 weeks (pNET) and 6.3 weeks (epNET) in CABINET<sup>8</sup>

**WITHHOLD<sup>1</sup>**  
CABOMETYX for intolerable Grade 2 or Grade 3 PPE

**WAIT<sup>1</sup>**  
Until improvement to ≤Grade 1

**RESTART<sup>1</sup>**  
▼ CABOMETYX at a reduced dose; reduce by 20 mg daily  
**Adult and pediatric patients ≥12 years of age and bodyweight ≥40 kg**  
▼ Lowest dose is 20 mg daily  
**Pediatric patients ≥12 years of age and bodyweight <40 kg**  
▼ Lowest dose is 20 mg every other day  
**If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX**

| NCI-CTCAE v5.0 Grading Identification: PPE <sup>14</sup> |  |
|--|--|
| Grade  | DESCRIPTION  |
| 1  | <ul style="list-style-type: none"><li>Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain</li></ul>   |
| 2  | <ul style="list-style-type: none"><li>Skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain</li><li>Limiting instrumental ADL<sup>a</sup></li></ul>     |
| 3  | <ul style="list-style-type: none"><li>Severe skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain</li><li>Limiting self-care ADL<sup>b</sup></li></ul> |

## Management tips for PPE/HFS

Advise patients to tell their health care provider if they experience any of the following early signs and manifestations of PPE/HFS<sup>16,17</sup>:

- 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)

### Supportive measures for PPE<sup>16,17</sup>:

- 20% urea cream twice daily and 0.05% clobetasol cream once daily
- Analgesics for pain control if needed for Grade 2 or above

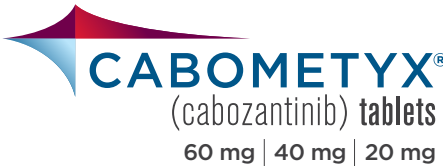
All patients should be advised on prophylactic skin care, including<sup>16</sup>:

- Use of hypoallergenic moisturizing creams or ointments
- Sunscreen with 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
- Careful monitoring of patients with skin disorders for signs of infection (eg, abscess, cellulitis, or impetigo)

Early and adequate interventions are recommended, including early referral to a dermatologist, to prevent worsening of skin symptoms, such as blisters, desquamation, ulcerations, or necrosis of affected areas.<sup>16</sup>

<sup>a</sup>Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.  
<sup>b</sup>Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

Please see additional **Important Safety Information** and **full Prescribing Information**.



# Fatigue<sup>a</sup>



## WITHHOLD<sup>1</sup>

CABOMETYX for intolerable Grade 2 or Grade 3-4 fatigue



## WAIT

Until improvement to baseline or ≤Grade 1



## RESTART<sup>1</sup>

▼ CABOMETYX at a reduced dose; reduce by 20 mg daily

**Adult and pediatric patients ≥12 years of age and bodyweight ≥40 kg**

▼ Lowest dose is 20 mg daily

**Pediatric patients ≥12 years of age and bodyweight <40 kg**

▼ Lowest dose is 20 mg every other day

**If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX**

### NCI-CTCAE v5.0 Grading Identification: **Fatigue**<sup>14</sup>

| Grade | DESCRIPTION  |
|-------|--|
| 1     | <ul style="list-style-type: none"><li>Fatigue relieved by rest</li></ul>   |
| 2     | <ul style="list-style-type: none"><li>Fatigue not relieved by rest</li><li>Limiting instrumental ADL<sup>b</sup></li></ul> |
| 3     | <ul style="list-style-type: none"><li>Fatigue not relieved by rest</li><li>Limiting self-care ADL<sup>c</sup></li></ul>    |

### Management tips for fatigue

**Advise patients to notify their health care provider immediately for any of the following<sup>18</sup>:**

- Too tired to get out of bed for 24-hour period
- Trouble waking up
- Trouble catching breath
- Fatigue seems to be worsening

#### Supportive measures for fatigue<sup>17</sup>

- 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

<sup>a</sup>Median time to first occurrence of fatigue was not available in CABINET.  
<sup>b</sup>Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.  
<sup>c</sup>Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.


**Please see additional Important Safety Information and full Prescribing Information.**



# Hypertension<sup>a</sup>

Median time to first occurrence of hypertension was 2.1 weeks (pNET and epNET) in CABINET<sup>8</sup>

Do not initiate CABOMETYX in patients with uncontrolled hypertension



**WITHHOLD<sup>1</sup>**

CABOMETYX for Grade 3 hypertension that is not adequately controlled



**WAIT<sup>1</sup>**

Until hypertension is adequately controlled to ≤Grade 2



**RESTART<sup>1</sup>**

▼ CABOMETYX at a reduced dose; reduce by 20 mg daily

**Adult and pediatric patients ≥12 years of age and bodyweight ≥40 kg**


▼ Lowest dose is 20 mg daily

**Pediatric patients ≥12 years of age and bodyweight <40 kg**

▼ Lowest dose is 20 mg every other day

**If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX**

| NCI-CTCAE v5.0 Grading Identification: Hypertension <sup>14</sup> |   |
|---|---|
| Grade   | DESCRIPTION   |
| 1   | <ul style="list-style-type: none"> <li>SBP 120-139 mm Hg or DBP 80-89 mm Hg</li> </ul>  |
| 2   | <ul style="list-style-type: none"> <li>SBP 140-159 mm Hg or DBP 90-99 mm Hg if previously within normal limit</li> <li>Change in baseline medical intervention indicated</li> <li>Recurrent or persistent (≥24 h)</li> <li>Symptomatic increase by &gt;20 mm Hg (DBP) or to &gt;140/90 mm Hg</li> <li>Antihypertensive monotherapy indicated</li> </ul> |
| 3   | <ul style="list-style-type: none"> <li>SBP ≥160 mm Hg or DBP ≥100 mm Hg</li> <li>Medical intervention indicated</li> <li>More than 1 drug or more intensive therapy than previously used indicated</li> </ul>   |
| 4   | <ul style="list-style-type: none"> <li>Life-threatening consequences (eg, malignant hypertension, transient or permanent neurological deficit, hypertensive crisis)</li> <li>Urgent intervention indicated</li> </ul>   |



**PERMANENTLY DISCONTINUE<sup>1</sup>**

CABOMETYX for Grade 3 hypertension that cannot be controlled with antihypertensive therapy or Grade 4 hypertension, including hypertensive crisis

**Management tips for hypertension**

**Advise patients to notify their health care provider if they develop<sup>1</sup>:** severe headaches, nosebleeds, tiredness or confusion, vision changes, chest pain, trouble breathing, irregular heartbeat, blood in the urine

**Supportive measures for hypertension<sup>1</sup>**


- Monitor blood pressure before initiation and regularly during treatment
- If needed, prescribe medication to treat hypertension

<sup>a</sup>Grouped term. Includes hypertension, blood pressure increased, blood pressure systolic increased, and systolic hypertension.<sup>1</sup>  
DBP, diastolic blood pressure; SBP, systolic blood pressure.


Please see additional Important Safety Information and full Prescribing Information.




# Elevated liver enzymes<sup>a</sup>



**WITHHOLD<sup>1</sup>**  
 CABOMETYX for intolerable Grade 2 or Grade 3-4 elevated liver enzymes



**WAIT<sup>1</sup>**  
 Until improvement to baseline or ≤Grade 1



**RESTART<sup>1</sup>**  
 ▼ CABOMETYX at a reduced dose; reduce by 20 mg daily  
  

**Adult and pediatric patients ≥12 years of age and bodyweight ≥40 kg**  
 ▼ Lowest dose is 20 mg daily

**Pediatric patients ≥12 years of age and bodyweight <40 kg**  
 ▼ Lowest dose is 20 mg every other day

  
**If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX**

NCI-CTCAE v5.0 Grading Identification: Increased ALT or AST<sup>14</sup>

| Grade | DESCRIPTION   |
|-------|---|
| 1     | <ul style="list-style-type: none"> <li>&gt;ULN-3.0 x ULN if baseline was normal</li> <li>1.5-3.0 x baseline if baseline was abnormal</li> </ul> |
| 2     | <ul style="list-style-type: none"> <li>&gt;3.0-5.0 x ULN</li> </ul>   |
| 3     | <ul style="list-style-type: none"> <li>&gt;5.0-20 x ULN</li> </ul>  |
| 4     | <ul style="list-style-type: none"> <li>&gt;20 x ULN</li> </ul>  |

## Management tips for elevated liver enzymes

**Advise patients to notify their health care provider right away if they develop symptoms of liver problems, including<sup>1</sup>:** yellowing of skin or whites of eyes, severe nausea or vomiting, pain on the right side of stomach area (abdomen), dark urine, bleeding or bruising more easily than normal

### Supportive measures for elevated liver enzymes<sup>17</sup>

- Frequent monitoring of transaminases should be considered
- Treatment should be held until the etiology is determined and abnormalities are corrected or stabilized at clinically acceptable levels
- If possible, hepatotoxic concomitant medications should be discontinued in patients who develop increased values of ALT, AST, or bilirubin
- Evaluation of patients with elevated transaminases or 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

<sup>a</sup>Median time to first occurrence of elevated liver enzymes was not available in CABINET.  
 ULN, upper limit of normal.

**Please see additional Important Safety Information and full Prescribing Information.**



# Indications and Important Safety Information



## INDICATIONS

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pNET.

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated epNET.

## IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

**Hemorrhage:** CABOMETYX can cause severe and fatal hemorrhages. The incidence of Grade 3-5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

**Perforations and Fistulas:** Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

**Thrombotic Events:** CABOMETYX can cause arterial or venous thromboembolic event. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events

**Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) 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; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

**Diarrhea:** CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to  $\leq$  Grade 1; resume at a reduced dose.

**Palmar-Plantar Erythrodysesthesia (PPE):** CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Proteinuria:** Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to  $\leq$  Grade 1 proteinuria; resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** CABOMETYX can cause ONJ and it occurred in <1% of treated patients. 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. Withhold CABOMETYX for development of ONJ until complete resolution; resume at a reduced dose.

# Indications and Important Safety Information



## IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS

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

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** CABOMETYX can cause RPLS. Perform evaluation for RPLS and diagnose by characteristic finding on MRI any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

**Thyroid Dysfunction:** CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism, and it occurred in 19% of treated patients (0.4% Grade 3). Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

**Hypocalcemia:** CABOMETYX can cause hypocalcemia, with the highest incidence in DTC patients. Based on the safety population, hypocalcemia occurred in 13% of CABOMETYX patients (2% Grade 3 and 1% Grade 4).

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume CABOMETYX at a reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

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

## ADVERSE REACTIONS

The most common ( $\geq 20\%$ ) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, and constipation.

## DRUG INTERACTIONS

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

**Strong or Moderate CYP3A4 Inducers:** If coadministration with strong or moderate 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. Avoid CABOMETYX in patients with severe hepatic impairment.

**Pediatric Use:** Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Physeal and longitudinal growth monitoring is recommended in children (12 years and older) with open growth plates. Consider interrupting or discontinuing CABOMETYX if abnormalities occur. The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

**Please see accompanying full [Prescribing Information](#).**

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.

## National Comprehensive Cancer Network<sup>®</sup> (NCCN) Recommendation<sup>19</sup>



**Cabozantinib (CABOMETYX) is a recommended systemic anti-tumor therapy for certain patients with:**

- Pancreatic NET (Grade 1/2)<sup>a</sup>
- Gastrointestinal tract NET (Grade 1/2)<sup>a</sup>
- Lung/thymus NET
- Grade 3 NET<sup>a</sup>

<sup>a</sup>Well-differentiated.



**VIEW THE NCCN  
RECOMMENDATIONS**

# Informing patients throughout their treatment journey about potential ARs and dose modifications helps set their expectations



**EDUCATE** patients on signs and symptoms of common adverse reactions (ARs)



**ENCOURAGE** patients to report signs and symptoms early, so the healthcare team can quickly address them



**HIGHLIGHT** the importance of early reporting in effective management of ARs and appropriate dosing modifications for efficacy and tolerability



**ADVISE** patients that their dose may need to be adjusted to help manage certain ARs



**ASSURE** patients that dose reductions may help them stay on treatment, as appropriate; they should not consider them setbacks

**It is important for patients to understand that treatment of advanced cancer involves finding the right dose that balances efficacy, safety, and tolerability<sup>20,21</sup>**



Exelixis Access Services® (EASE) provides a variety of support to help your patients start treatment quickly. EASE can help meet the unique needs of your patients and practice at each step along the access journey.



YOUR EASE CASE MANAGER



EASE offers regionally dedicated Case Managers as a single point of contact.

- Offers **prompt support** with payer coverage, financial assistance, and treatment coordination
- Can **provide the status** of your patients' access journey
- Provides **proactive follow-up**

Complete enrollment by visiting:  
**www.EASE.US**  
EASE will confirm your patient's eligibility for requested services.

HELP PATIENTS START AND STAY ON CABOMETYX® (cabozantinib)



30-Day Free Trial Program

Provides a free trial to help new CABOMETYX patients start treatment quickly, regardless of insurance type, with a 30-day additional supply available for patients with a payer decision delay of 5 days or more.<sup>a,b</sup>



Co-Pay Program

Eligible, commercially insured patients **may pay as little as \$0 per month**. Annual and transaction limits apply.<sup>c</sup>



Dose Exchange Program


Provides **a free 15-tablet supply in the lower dose** to help patients who require a dose reduction.<sup>b,d</sup>




Patient Assistance Program

Eligible patients who cannot afford their drug costs may receive CABOMETYX **free of charge**.<sup>b</sup>

CONTACT EASE FOR MORE INFORMATION AND TO ENROLL

 **CALL: 1-844-900-EASE** (1-844-900-3273)  
Monday to Friday, 8:00 AM to 8:00 PM (ET)

 **FAX: 1-844-901-EASE**  
(1-844-901-3273)

 **VISIT: www.EASE.US**

SUPPORT FOR COVERAGE DETERMINATION



At your request, EASE can provide support with:

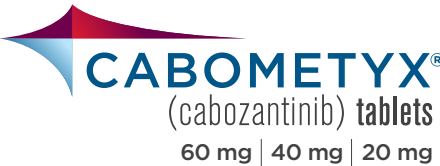
- **Benefits investigations**
- **Prior authorization assistance<sup>e</sup>**
- **Appeals support and follow-up**

<sup>a</sup>Limited to on-label indications. <sup>b</sup>Additional restrictions and eligibility rules apply. <sup>c</sup>The Co-Pay Program is not available to patients receiving prescription reimbursement under any federal, state, or government-funded insurance programs or where prohibited by law. Additional [Terms and Conditions](#) apply. <sup>d</sup>Patients are required to return any unused product. <sup>e</sup>CoverMyMeds can also be utilized for enrollment and prior authorization support.

This description of the Exelixis Access Services® 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 healthcare provider, legal counsel, or applicable third-party payer(s). Exelixis reserves the right to modify the program at any time without notice.

CoverMyMeds is a registered trademark of CoverMyMeds, LLC.

Please see additional [Important Safety Information](#) and [full Prescribing Information](#).



## Encourage your patients and caregivers to sign up for



A free support program with tools and resources to help educate patients and caregivers during treatment with CABOMETYX

### Your patients may sign up to learn more about what they may expect while on treatment with CABOMETYX

- ✓ Recognizing side effects and working with their health care team
- ✓ Lifestyle tips offering wellness support
- ✓ Where to find useful resources
- ✓ Information about organizations that may offer support

“ The CABOMETYX BE CONNECTED program is especially useful to a number of our patients. The support they provide, the education... [It] really does benefit patients in a multitude of ways. ”

— From a doctor who encourages his patients to sign up for BE CONNECTED

### SIGNING UP IS EASY



#### ONLINE

Go to:

[cabometyx.com/be-connected](http://cabometyx.com/be-connected)



#### MAIL

Complete and return the **sign-up card included in the Patient Care Kit**

To request a Patient Care Kit, contact your local CABOMETYX sales representative<sup>a</sup>

<sup>a</sup>Limit one Patient Care Kit per patient. US residents only. Additional restrictions and eligibility rules apply. Exelixis may at its sole option modify these terms and conditions without notice.


Please see additional **Important Safety Information** and **full Prescribing Information**.






CABOMETYX provides a balance of efficacy and safety data to a broad NET population<sup>1</sup>

CABOMETYX is the first and only FDA-approved treatment for previously treated patients with NET, regardless of site of origin and functional status<sup>1-6</sup>




**CABOMETYX quadrupled median PFS in pNET<sup>1,7</sup>**

- Median PFS: 13.8 months (95% CI, 8.9-17.0; n=66) vs 3.3 months with placebo (95% CI, 2.8-5.7; n=33); HR, 0.22 (95% CI, 0.12-0.41); *P*<.0001



**CABOMETYX doubled median PFS in epNET<sup>1,7</sup>**

- Median PFS: 8.5 months (95% CI, 6.8-12.5; n=132) vs 4.2 months with placebo (95% CI, 3.0-5.7; n=67); HR, 0.40 (95% CI, 0.26-0.61); *P*<.0001



**The safety profile observed in CABINET was consistent with the known CABOMETYX safety profile<sup>1,7</sup>**

- No new safety signals were observed in CABINET
- The 5 most common any-grade ARs across cohorts were fatigue, increased AST, increased ALT, hypertension, and diarrhea

INDICATIONS

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pNET.

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated epNET.

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, palmar-plantar erythrodysesthesia, proteinuria, osteonecrosis of the jaw, impaired wound healing, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, hypocalcemia, and embryo-fetal toxicity.

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