רופא/ה, רוקח/ת נכבדים,

הריני להודיעכם כי העלון של התכשיר עודכן:

Cabometyx 20 mg	**קבומטיקס 20 מ"ג**
Cabometyx 40 mg	**קבומטיקס 40 מ"ג**
Cabometyx 60 mg	**קבומטיקס 60 מ"ג**

Film-coated tablets

CABOMETYX 20 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 20 mg cabozantinib.
Excipients with known effect
Each film-coated tablet contains 15.54 mg lactose.

CABOMETYX 40 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 40 mg cabozantinib.
Excipients with known effect
Each film-coated tablet contains 31.07 mg lactose.

CABOMETYX 60 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 60 mg cabozantinib.
Excipients with known effect
Each film-coated tablet contains 46.61 mg lactose

התוויות מאושרות:

Renal Cell Carcinoma (RCC)
CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC):
- in treatment-naïve adults with intermediate or poor risk, per IMDC criteria.
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Hepatocellular Carcinoma (HCC)
CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC), in adults with Child-Pugh Class A hepatic impairment who have previously been treated with sorafenib.

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להלן העדכונים בעלון לרופא המהווים החמרה (מסומנים בצהוב):

4.2 Posology and method of administration

RCC: Patients with hepatic impairment
[…]
Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2).
[...]
HCC: patients with hepatic impairment
CABOMETYX is indicated to adult patients with mild hepatic impairment (Child Pugh A)

4.4 Special warnings and precautions for use

As most events occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted.
[…]
In hepatocellular carcinoma following prior systemic therapy, dose reductions and dose interruptions occurred in 62% and 84%, respectively, of cabozantinib-treated patients in the clinical trial (CELESTIAL). Two dose reductions were required in 33% of patients. The median time to first dose reduction was 38 days, and to first dose interruption was 28 days. Closer monitoring is advised in patients with mild or moderate hepatic impairment.

Hepatic effects
Abnormalities of liver function tests (increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with cabozantinib. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening of liver function tests considered related to cabozantinib treatment (i.e. where no alternative cause is evident), the dose modification advice in Table 1 should be followed (see section 4.2).
[…]
Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Cabometyx is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as cabozantinib has not been studied in this population and exposure might be increased in these patients.

Hepatic encephalopathy
In the HCC study (CELESTIAL), hepatic encephalopathy was reported more frequently in the cabozantinib than the placebo arm. Cabozantinib has been associated with diarrhoea, vomiting, decreased appetite and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Patients should be monitored for signs and symptoms of hepatic encephalopathy.

Gastrointestinal (GI) disorders
Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI adverse reactions (see section 4.8). Prompt medical management, including supportive care with antiemetics, antidiarrhoeals, or antacids, should be instituted to prevent dehydration, electrolyte imbalances and weight loss. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant GI adverse reactions (see Table 1).

Thromboembolic events
Events of venous thromboembolism, including pulmonary embolism, and arterial thromboembolism, sometimes fatal, have been observed with cabozantinib. […] In the HCC study (CELESTIAL), portal vein thrombosis was observed with cabozantinib, including one fatal event. Patients with a history of portal vein invasion appeared to be at higher risk of developing portal vein thrombosis. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant thromboembolic complication.

Haemorrhage
Severe haemorrhage, sometimes fatal, has been observed with cabozantinib.
[…]
In the HCC study (CELESTIAL), fatal haemorrhagic events were reported at a higher incidence with cabozantinib than placebo. Predisposing risk factors for severe haemorrhage in the advanced HCC population may include tumour invasion of major blood vessels and the presence of underlying liver cirrhosis resulting in oesophageal varices, portal hypertension, and thrombocytopenia.
[…]

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Thrombocytopenia
In the HCC study (CELESTIAL), thrombocytopenia and decreased platelets were reported. Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia (see Table 1).
[…]
Biochemical laboratory test abnormalities
Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, hyponatremia). It is recommended to monitor biochemical parameters during cabozantinib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Cases of hepatic encephalopathy in HCC patients can be attributed to the development of electrolyte disturbances. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant abnormalities (see Table 1).

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Summary of safety profile
The most common serious adverse drug reactions in the RCC population (≥1% incidence) are diarrhoea, hypertension, dehydration, hyponatraemia, nausea, decreased appetite, embolism, …

The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, palmar-plantar erythrodysaesthesia syndrome, asthenia and diarrhoea.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, palmar-plantar erythrodysaesthesia syndrome, fatigue, decreased appetite hypertension and nausea.

Table 2: Adverse drug reactions (ADRs) reported in clinical trials in patients treated with cabozantinib

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Vascular disorders	hypertension, haemorrage	venous thrombosis arterial thrombosis		Aneurysms and artery dissections
Gastrointestinal disorders	[…] dyspepsia, upper abdominal pain	gastrointestinal perforation, fistula, gastroesophageal reflux disease, […]	pancreatitis, glossodynia	
Hepatobiliary disorders		Hepatic encephalopathy	hepatitis cholestatic	
General disorders and administration site conditions	[…] asthenia, peripheral oedema			

Description of selected adverse reactions
Data for the following reactions are based on patients who received Cabometyx 60 mg qd po in the pivotal studies in RCC following prior VEGF-targeted therapy and in treatment-naïve RCC and in HCC following prior systemic therapy (section 5.1).

Gastrointestinal (GI) perforation
[...]
In the HCC study (CELESTIAL), GI perforations were reported in 0.9% of cabozantinib-treated patients (4/467). All events were Grade 3 or 4. Median time to onset was 5.9 weeks.
[…]

Hepatic encephalopathy
In the HCC study (CELESTIAL), hepatic encephalopathy (hepatic encephalopathy, encephalopathy, hyperammonaemic encephalopathy) was reported in 5.6% of cabozantinib-treated patients (26/467); Grade 3-4 events in 2.8%, and one (0.2%) Grade 5 event. Median time to onset was 5.9 weeks.
[…]

Diarrhoea
In the study in RCC following prior VEGF-targeted therapy (METEOR), diarrhoea was reported in 74% of cabozantinib-treated RCC patients (245/331); Grade 3-4 events in 11%. . Median time to onset was 4.9 weeks.
In the treatment-naïve RCC study (CABOSUN), diarrhoea was reported in 73% of cabozantinib treated patients (57/78);Grade 3-4 events in 10%..
In the HCC study (CELESTIAL), diarrhoea was reported in 54% of cabozantinib-treated patients (251/467);Grade 3- 4 events in 9.9%. Median time to onset of all events was 4.1 weeks. Diarrhoea led to dose modifications, interruptions and discontinuations in 84/467 (18%), 69/467 (15%) and 5/467 (1%) of subjects, respectively.

Fistulas
[…]
In the HCC study (CELESTIAL), fistulas were reported in 1.5% (7/467) of the HCC patients. Median time to onset was 14 weeks.
Fatal fistulas have occurred in the cabozantinib clinical program

Haemorrhage
[…]
In the HCC study (CELESTIAL), the incidence of severe haemorrhagic events (Grade ≥ 3) was 7.3% in cabozantinib-treated patients (34/467). Median time to onset was 9.1 weeks.
[…]

להלן העדכונים בעלון לצרכן המהווים החמרה (מסומנים בצהוב):

2. לפני השימוש בתרופה
[...]
לפני הטיפול בקבומטיקס, ספר לרופא או לרוקח אם:
[...]
- אתה סובל או סבלת בעבר ממפרצת (התרחבות והיחלשות של דופן כלי הדם) או קרע בדופן כלי הדם
[...]

4. תופעות לוואי
[...]
פנה מיד לרופא אם אתה מבחין באחת מתופעות הלוואי הבאות – ייתכן שתזדקק לטיפול רפואי דחוף:
[...]
- תחושת רדימות, בלבול או אובדן הכרה. זה עלול לנבוע מבעיות כבד.

תופעות לוואי אחרות כוללות:

תופעות לוואי שכיחות מאוד (עלולות להשפיע על יותר מ-1 מתוך 10 אנשים):
[...]
- שינויים בבדיקות הדם המשמשות לניטור הבריאות הכללית ותפקוד האיברים (כולל הכבד והכליות), [...]

[...]
- נפיחות ברגליים ובזרועות

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תופעות לוואי שכיחות (עלולות להשפיע על עד 1 מתוך 10 אנשים):

[...]

- רמות נמוכות של טסיות ותאי דם לבנים
- רמות נמוכות של אלבומין בדם
- עליה או ירידה ברמות הסוכר בדם

[...]

- קרע כואב או חיבור לא תקין של הרקמות בגוף

[...]

- תחושת רדימות, בלבול או אובדן הכרה עקב בעיות כבד
- עור יבש, גירוד חמור של העור, אקנה

[...]

תופעות לוואי שאינן שכיחות (עלולות להשפיע על 1 מתוך 100 אנשים):

[...]

- רמות נמוכות של סוג מסוים של תאי דם לבנים (לימפוציטים)
- תחושת צריבה או עקצוץ בלשון

[...]

- עליה ברמות הטריגליצרידים בדם

[...]

תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה):

[...]

- התרחבות והיחלשות של דופן כלי דם או קרע בדופן כלי דם (מפרצות וביתור עורקי)

[...]

העלון לרופא והעלון לצרכן נמצאים בקישור וכן נשלחו לפרסום במאגר התרופות באתר משרד הבריאות וניתן לקבלם מודפס על ידי פניה לבעל הרישום.

בברכה,
חיה שליו

מגר' חיה שליו
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רוקחת ממונה
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