Cabozantinib (Cabometyx)
Manufacturer: Exelixis, Inc., South San Francisco, California
Date of Approval: April 25, 2016
Indication: Cabozantinib is used for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.
Drug Class: Tyrosine kinase inhibitor

Uniqueness of Drug: Cabozantinib is the only drug approved to treat advanced RCC that provides a statistically significant improvement in overall survival (OS), progression-free survival (PFS), and overall response rate.

Warnings and Precautions:
Hemorrhage. Severe and fatal hemorrhages have occurred with cabozantinib treatment. Do not administer cabozantinib to patients who have or are at risk for severe hemorrhage.

Gastrointestinal (GI) perforations and fistulas. In a randomized study in RCC, fistulas were reported in 1.2% (including 0.6% anal fistulas) of patients treated with cabozantinib and 0% of patients treated with everolimus (Afinitor, Novartis). Monitor for symptoms and discontinue cabozantinib if fistulas or GI perforations that cannot be adequately managed occur.

Thrombotic events. Cabozantinib treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of cabozantinib-treated patients versus 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of cabozantinib-treated patients versus 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of cabozantinib-treated patients and 0.3% of everolimus-treated patients. Fatal thrombotic events occurred in the Cabometyx clinical program. Discontinue cabozantinib if myocardial infarction, cerebral infarction, or other serious arterial thromboembolic events occur.

Hypertension and hypertensive crisis. Cabozantinib treatment results in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% grade 3 or higher) of cabozantinib-treated patients and 7.1% (3.1% grade 3 or higher) of everolimus-treated patients. Monitor blood pressure prior to initiation and regularly during treatment. Withhold cabozantinib for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue cabozantinib for severe hypertension that cannot be controlled with antihypertensive therapy or if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

Diarrhea. Diarrhea occurred in 74% of patients treated with cabozantinib and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of cabozantinib-treated patients and in 2% of everolimus-treated patients. Withhold cabozantinib in patients who develop intolerable grade 2 diarrhea or grade 3 or 4 diarrhea that cannot be managed with standard antidiarreal treatments until improvement to grade 1; resume cabozantinib at a reduced dose.

Palmar-plantar erythrodysesthesia syndrome (PPES). PPES, which causes redness, swelling, and pain on the palms of the hands and/or the soles of the feet, occurred in 42% of patients treated with cabozantinib and in 6% of patients treated with everolimus. Interrupt cabozantinib treatment until PPES resolves or decreases to grade 1.

Reversible posterior leukoencephalopathy syndrome (RPLS). Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue cabozantinib in patients who develop RPLS.

Embryo-fetal toxicity. Advise pregnant women of the potential risk to a fetus, and advise women of reproductive potential to use effective contraception during treatment with cabozantinib and for four months after the last dose.

Dosage and Administration: Do not substitute tablets with capsules. The recommended dose of cabozantinib is one 60-mg tablet once daily. Patients should not eat for at least two hours before and at least one hour after taking cabozantinib. The tablets should not be crushed. A missed dose should not be taken within 12 hours of the next dose. Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during cabozantinib treatment.

Dosage Adjustments:
For patients undergoing surgery. Stop treatment with cabozantinib at least 28 days prior to scheduled surgery, including dental surgery.

For adverse reactions. Using the National Cancer Institute’s “Common Terminology Criteria for Adverse Events,” withhold cabozantinib for grade 4 adverse reactions and for grade 3 or intolerable grade 2 adverse reactions that cannot be managed with a dose reduction or supportive care.

Upon resolution or improvement (i.e., return to baseline or resolution to grade 1) of an adverse reaction, reduce the dose as follows:

- If previously receiving 60 mg daily, resume treatment at 40 mg daily.
- If previously receiving 40 mg daily, resume treatment at 20 mg daily.
- If previously receiving 20 mg daily, resume at 20 mg daily if tolerated, otherwise, discontinue cabozantinib.

Permanently discontinue cabozantinib in the case of development of unmanageable fistulae or GI perforation, or severe hemorrhage.

Commentary: The approval of Cabometyx was based on findings from the 658-patient phase 3 METEOR trial, in which cabozantinib was shown to improve overall survival (OS), progression-free survival (PFS), and overall response rate compared to everolimus. The approval was based on findings from the 658-patient phase 3 METEOR trial, in which cabozantinib was shown to improve overall survival (OS), progression-free survival (PFS), and overall response rate compared to everolimus.

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which the drug demonstrated a 42% reduction in the risk of progression or death compared with everolimus in patients with advanced RCC. After a minimum of 11 months of follow-up, median PFS was 7.4 months for cabozantinib compared with 3.8 months for everolimus. Cabozantinib also reduced the risk of death by 34% in the intent-to-treat population. Median OS was 21.4 months for patients receiving cabozantinib versus 16.5 months for those receiving everolimus. The most commonly reported adverse reactions occurring in 25% or more of patients were diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, decreased weight, and constipation.

Sources: Exelixis, Inc.; Cabometyx prescribing information

**Glycopyrrolate and Formoterol Fumarate (Bevespi Aerosphere)**

**Manufacturer:** AstraZeneca Pharmaceuticals, Wilmington, Delaware

**Date of Approval:** April 25, 2016

**Indication:** Bevespi Aerosphere is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting beta, agonist (LABA). It is an inhalation aerosol used for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/ or emphysema.

**Drug Class:** Long-acting muscarinic antagonist (LAMA)/long-acting beta, agonist (LABA)

**Uniqueness of Drug:** Glycopyrrolate/formoterol fumarate is the first dual bronchodilator in a pressurized metered-dose inhaler, delivered using unique formulation technology

**Warnings and Precautions:**

- **Boxed warning:** LABAs increase the risk of asthma-related death. Glycopyrrolate/formoterol fumarate is not indicated for the treatment of asthma.
- **Deterioration of disease and acute episodes.** Do not initiate this medication in patients with acutely deteriorating COPD, which may be a life-threatening condition.
- **Excessive use and use with other LABAs.** Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medications. Patients should not use another LABA with glycopyrrolate/formoterol fumarate for any reason.
- **Paradoxical bronchospasm.** If paradoxical bronchospasm occurs following dosing with glycopyrrolate/formoterol fumarate, it should be treated immediately with an inhaled, short-acting bronchodilator. Discontinue glycopyrrolate/formoterol fumarate and institute alternate therapy.
- **Immediate hypersensitivity reactions.** Discontinue this medication immediately if there are any signs of allergic reactions, especially angioedema (including difficulties in breathing, swallowing, swelling of tongue, lips, and face), urticaria, or skin rash.
- **Cardiovascular effects.** Use with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- **Coexisting conditions.** Use with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines.
- **Hypokalemia and hyperglycemia.** Be alert to changes in potassium and glucose levels.

**Worsening of narrow-angle glaucoma.** Use with caution in patients with narrow-angle glaucoma. Be alert for signs and symptoms of acute narrow-angle glaucoma (eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema).

**Worsening of urinary retention.** Use with caution in patients with urinary retention. Be alert for signs and symptoms of urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction.

**Dosage and Administration:** For maintenance treatment of COPD, two inhalations of glycopyrrolate/formoterol fumarate should be taken twice daily. It is for oral inhalation only.

**Commentary:** The approval of the therapy was based on the PINNACLE trial, which demonstrated that Bevespi Aerosphere achieved statistically significant improvement in morning predose forced expiratory volume in one second at 24 weeks ($P < 0.001$) versus its mono-components and placebo. The most common adverse reactions with glycopyrrolate/formoterol fumarate (with a 2% or greater incidence and more common than with placebo) were urinary tract infection (2.6% versus 2.3% with placebo) and cough (4.0% versus 2.7% with placebo).

Sources: AstraZeneca Pharmaceuticals; Bevespi Aerosphere prescribing information

**Ephedrine Sulfate Injection, USP (Akovaz)**

**Manufacturer:** Flamel Technologies, Lyons, France

**Date of Approval:** May 2, 2016

**Indication:** Ephedrine sulfate injection is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent that is used for the treatment of clinically important hypotension occurring in the setting of anesthesia.

**Drug Class:** Adrenergic and dopaminergic agents

**Uniqueness of Drug:** Ephedrine sulfate is the first drug to receive approval from the Food and Drug Administration for the treatment of hypotension in the event of a crisis following a surgical procedure. Hypotension is one of the most common intraoperative crisis incidents during surgery and has been associated with devastating perioperative complications, such as stroke and myocardial infarction.

**Warnings and Precautions:**

- **Pressor effect with concomitant oxytocic drugs.** Serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine). Some of these patients experienced stroke. Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.
- **Tolerance and tachyphylaxis.** Data indicate that repeated administration of ephedrine can result in tachyphylaxis. Clinicians treating anesthesia-induced hypotension with ephedrine should be aware of the possibility of tachyphylaxis and should be prepared with an alternative pressor to mitigate unacceptable responsiveness.
- **Risk of hypertension when used prophylactically.** When used to prevent hypotension, ephedrine has been associated with an increased incidence of hypertension compared to when it is used to treat hypotension.

**Dosage and Administration:** Ephedrine sulfate injection, 50 mg/mL (equivalent to 38 mg ephedrine base), must be continued on page 561
diluted before administration as an intravenous (IV) bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water according to manufacturer instructions.

The recommended dose for the treatment of clinically important hypotension in the setting of anesthesia is initially 5–10 mg, administered by IV bolus. Administer additional boluses as needed, not to exceed a total dosage of 50 mg. Adjust dosage according to the blood pressure goal (i.e., titrate to effect).

**Commentary:** The evidence for the efficacy of ephedrine injection is derived from the published literature. Increases in blood pressure following administration of ephedrine were observed in 14 studies, including nine in which ephedrine was used in pregnant women undergoing neuraxial anesthesia during Cesarean delivery, one study in nonobstetrical surgery under neuraxial anesthesia, and four studies in patients undergoing surgery under general anesthesia. Ephedrine has been shown to raise systolic and mean blood pressure when administered as a bolus dose following the development of hypotension during anesthesia. The most common adverse reactions during treatment included nausea, vomiting, and tachycardia.

**Sources:** Flamel Technologies, Akovaz prescribing information