

Pharmaceutical Approval Update

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Cabozantinib (Cometriq) Capsules

Manufacturer: Exelixis, Inc., San Francisco, Calif.

Indication: Cabozantinib is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer.

Drug Class: Cabozantinib (S)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate. The drug's molecular weight is 635.6 daltons as malate salt.

Uniqueness of Drug: Cabozantinib is a kinase inhibitor that blocks abnormal kinase proteins involved in the development and growth of medullary cancer cells. *In vitro* assays have shown that cabozantinib inhibits the tyrosine kinase activity of RET; MET; VEGFR-1, -2, and -3; KIT; TRKB; FLT-3; AXL; and TIE-2. These receptor tyrosine kinases (RTKs) are involved in both normal cellular function and pathological processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

Boxed Warning:

Perforations and fistulas. Gastrointestinal (GI) perforations occurred in 3% of cabozantinib-treated patients and fistula formation occurred in 1%. Therapy should be discontinued in patients with GI perforations or fistulas.

Hemorrhage. Severe, sometimes fatal hemoptysis and GI hemorrhage occurred in 3% of cabozantinib-treated patients. Patients should be monitored for signs and symptoms of bleeding. Cabozantinib should not be administered to patients with severe hemorrhage.

Warnings and Precautions:

Perforations and fistulas. GI perforations and fistulas have been reported in cabozantinib-treated patients. All events were serious, and one GI fistula was fatal. Non-GI tracheal-esophageal fistulas have also been reported, with two fistulas proving fatal. Patients should be monitored for symptoms of perforations and fistulas. Patients with perforations or fistulas should not take cabozantinib.

Hemorrhage. Serious and sometimes fatal hemorrhage has occurred with cabozantinib. More grade 3 hemorrhagic events have occurred with cabozantinib than with placebo (3% vs. 1%, respectively). Cabozantinib should be avoided in patients with a recent history of hemorrhage or hemoptysis.

Thrombotic events. Therapy with cabozantinib has resulted in an increased incidence of thrombotic events, such as venous thromboembolism (VTE), in 6% of treated patients versus 3% of placebo patients. Arterial thromboembolism has been reported in 2% of treated patients versus 0% in placebo patients. Cabozantinib should be discontinued if an acute myocardial infarction (MI) or any other clinically significant arterial thromboembolic complication develops.

Wound complications. Wound sequelae have been reported with cabozantinib. Treatment should be stopped at least 28 days before scheduled surgery. Cabozantinib may be resumed after surgery if wound healing is judged to be adequate. The drug should be withheld in patients with dehiscence or wound-healing complications for which medical intervention is necessary.

Hypertension. In a randomized trial, cabozantinib resulted in an increased incidence of treatment-emergent hypertension stage 1 or 2 in 61% of cabozantinib-treated patients compared with 30% of placebo-treated patients. Blood pressure (BP) should be monitored before the start of therapy and regularly during treatment. The medication should be withheld if BP is not adequately controlled with medical management. After BP is controlled, cabozantinib may be resumed at a reduced dose. Cabozantinib should be discontinued if severe hypertension cannot be controlled with antihypertensive therapy.

Osteonecrosis of the jaw. In a clinical trial, osteonecrosis of the jaw (ONJ) occurred in 1% of cabozantinib-treated patients. Symptoms can include 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. An oral examination should be conducted before cabozantinib therapy begins and periodically during treatment. Patients should be advised to follow good oral hygiene practices.

Palmar-plantar erythrodysesthesia syndrome. In a trial, 50% of patients receiving cabozantinib experienced hand-foot syndrome, which was severe (grade 3) in 13% of these patients. Cabozantinib should be withheld if an intolerable grade 2, 3, or 4 reaction develops until improvement to grade 1 occurs. Treatment can then be resumed at a reduced dose.

Proteinuria. Proteinuria was observed in 2% of patients receiving cabozantinib, including one patient with nephrotic syndrome. Proteinuria did not develop with placebo. Urinary protein should be monitored regularly during treatment. Therapy should be stopped if nephrotic syndrome occurs.

Reversible posterior leukoencephalopathy syndrome. Subcortical vasogenic edema, which is diagnosed by magnetic resonance imaging, occurred in one patient. Patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function should be evaluated, and therapy should be discontinued if symptoms develop.

Hepatic impairment. Cabozantinib is not recommended for use in patients with moderate or severe hepatic impairment.

Dosage and Administration: The recommended dose of cabozantinib is 140 mg once daily (one 80-mg and three 20-mg capsules). The capsules should not be taken with food, and patients should not eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Treatment may be continued until disease progression or unacceptable toxicity occurs. The capsules should be swallowed whole, and they should not be opened. A missed dose should not be taken within 12 hours of the next dose. Patients should not ingest foods (e.g., grapefruit



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or grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 (CYP450) during cabozantinib therapy.

Dose adjustments. Cabozantinib should be withheld if grade 4 hematological adverse reactions, grade 3 or greater nonhematological adverse reactions, or intolerable grade 2 adverse reactions occur. When the adverse reaction resolves (i.e., a return to baseline values or to grade 1), the dose may be reduced, depending on physician orders. Cabozantinib should be permanently discontinued if patients experience visceral perforation, fistula formation, severe hemorrhage, a serious arterial thromboembolic event (e.g., MI, cerebral infarction), nephrotic syndrome, malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management, jaw osteonecrosis, or reversible posterior leukoencephalopathy syndrome.

Drug interactions:

CYP3A4 inhibitors. Cabozantinib should be avoided with the concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole). For patients needing treatment with a strong CYP3A4 inhibitor, the daily cabozantinib dose should be reduced by 40 mg. The dose that was used before CYP3A4 inhibitor therapy was initiated can be resumed 2 to 3 days after the strong inhibitor is discontinued.

CYP3A4 inducers. Cabozantinib should be avoided with the concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if an alternative therapy is available. Patients should avoid foods or nutritional supplements, such as St. John's wort (*Hypericum perforatum*), that induce CYP450 activity. For patients who require treatment with a strong CYP3A4 inducer, the daily dose of cabozantinib may be increased by 40 mg as tolerated. The dose that was used prior to initiating the CYP3A4 inducer may be resumed 2 to 3 days after the strong inducer is discontinued. The daily dose of cabozantinib should not exceed 180 mg.

Commentary: Medullary thyroid cancer develops in the thyroid cells that make calcitonin, a hormone that helps to maintain appropriate serum calcium levels. Vandetanib (Caprelsa, formerly Zactima, AstraZeneca), another drug for this condition, was approved in 2011 and reflects the FDA's commitment to the development and approval of drugs for treating rare diseases. Cabozantinib (Cometriq) received an orphan drug designation.

The National Cancer Institute estimated that thyroid cancer would be diagnosed in 56,460 Americans and would cause almost 1,800 deaths in 2012.

Cabozantinib can cause serious adverse effects that can lead to death, including severe hemorrhage, and GI perforations and fistulas. Patients should inform their health care practitioners if they experience severe abdominal pain or coughing, gagging, and choking, especially when they are eating or drinking.

In the pivotal study leading to the drug's approval, mean progression-free survival was 11.2 months with therapy and 4 months for placebo; however, cabozantinib did not extend life.

Sources: www.fda.gov; www.cometriq.com

Ponatinib (Iclusig) Tablets

Manufacturer: Ariad Pharmaceuticals, Cambridge, Mass.

Indication: Ponatinib is approved to treat two forms of

leukemia in adults who have not responded to prior tyrosine kinase inhibitor (TKI) therapy: chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL).

Drug Class: Ponatinib is a Bcr-Abl inhibitor that also selectively blocks other tyrosine kinases, including FLT3, RET, KIT, and the members of the fibroblast growth factor receptor (FGFR) and platelet-derived growth factor (PDGFR) families. The primary target is Bcr-Abl, an abnormal tyrosine kinase that is expressed in CML and Ph+ ALL.

Uniqueness of Drug: Ponatinib is designed with very high potency and broad specificity to block Bcr-Abl activity. It targets not only native Bcr-Abl but also its isoforms that carry mutations that confer resistance to treatment with existing TKIs, including the *T315I* mutation, for which no effective therapy currently exists.

Boxed Warning: Serious and fatal cases of arterial thrombosis and liver injury have occurred during treatment. Liver function should be monitored before and during treatment. Complete blood counts are recommended every 2 weeks during the first 3 months of therapy, then monthly or as needed thereafter.

Warnings and Precautions:

Thrombosis and thromboembolism. Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction (MI) and stroke have occurred in treated patients. MI or worsening coronary artery disease was the most common arterial thrombosis event, occurring in 5% of treated patients.

Serious cerebrovascular events have been noted in 2% of treated patients, with hemorrhagic conversion of the initial ischemic event and stenosis of large arterial vessels of the brain.

Serious peripheral arterial events were reported in 2% of treated patients. Some patients with diabetes and peripheral arterial disease experienced digital or distal extremity necrosis and required amputations.

Thirty of 34 study patients who experienced a serious arterial thrombosis event had one or more cardiovascular risk factors (e.g., MI, coronary artery disease, angina, stroke, transient ischemic attack, hypertension, diabetes mellitus, hyperlipidemia, smoking). Patients with cardiovascular risk factors are at an increased risk of arterial thrombosis with ponatinib. Therapy should be stopped or interrupted if arterial thrombotic events occur.

Venous thromboembolism. Venous thromboembolism (VTE), including deep vein thrombosis, pulmonary embolism, portal vein thrombosis, and retinal vein thrombosis, have been reported in treated patients. Modifying the dose or stopping therapy should be considered if serious VTE develops.

Congestive heart failure. Twenty treated patients (4%) experienced serious congestive heart failure (CHF) or left ventricular dysfunction, and four patients died. Patients should be monitored for signs or symptoms consistent with CHF and treated as clinically indicated, including interruption of treatment. Therapy should be stopped if serious CHF develops.

Hypertension. Eight of 449 patients who received ponatinib (2%) experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis.

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In 300 of 449 patients receiving ponatinib (67%), treatment-emergent hypertension occurred as described in the prescribing information, suggesting that it was not as serious as that found in the eight patients. Elevations in blood pressure (BP) should be monitored and managed.

Pancreatitis. Clinical pancreatitis occurred in 6% of ponatinib-treated patients (5% with grade 3), and lipase elevations occurred in 41%. Serum lipase levels should be checked every 2 weeks for the first 2 months, then monthly thereafter or as indicated. It may be necessary to interrupt or reduce the dose. If lipase elevations are accompanied by abdominal symptoms, treatment should be interrupted and patients should be evaluated for pancreatitis.

Hemorrhage. Serious bleeding, including fatalities, occurred in 5% of treated patients. The incidence was higher in patients with accelerated-phase and blast-phase CML and in those with Ph+ ALL. Most events occurred in patients with grade 4 thrombocytopenia. Therapy should be interrupted if serious or severe hemorrhage occurs.

Fluid retention. Severe fluid retention occurred in 3% of treated patients, and one instance of brain edema was fatal. Patients should be monitored for fluid retention and managed as clinically indicated. Therapy should be interrupted, reduced, or discontinued if indicated.

Cardiac arrhythmias. Three ponatinib-treated patients experienced bradyarrhythmias that led to the need for a pacemaker. Patients should be advised to report fainting, dizziness, or chest pain. Supraventricular tachyarrhythmias, including atrial fibrillation, occurred in 5% of ponatinib-treated patients. Patients should be advised to report palpitations or dizziness.

Myelosuppression. Severe myelosuppression (grade 3 or 4) occurred in 48% of treated patients. Complete blood counts should be obtained every 2 weeks for the first 3 months, then monthly or as indicated. The dose should be adjusted as recommended.

Tumor lysis syndrome. Two ponatinib patients with advanced CML developed serious tumor lysis syndrome. Hyperuricemia occurred in 7% of patients, and most of these patients had chronic CML. Patients should have adequate hydration, and high uric acid levels should be treated before therapy is initiated.

Poor wound healing and GI perforation. Because ponatinib may compromise wound healing, therapy should be interrupted at least 1 week before major surgery. Serious GI perforation occurred in one patient 38 days after cholecystectomy.

Embryofetal toxicity. Ponatinib may cause fetal harm. Women should be advised to avoid pregnancy while taking ponatinib. The drug caused embryofetal toxicity in rats at exposures lower than human exposures at the recommended human dose. If this drug is used during pregnancy or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

Dosage and Administration: The recommended dose of ponatinib is 45 mg once daily with or without food. Treatment may be continued until disease progression or unacceptable toxicity occurs. Dosage interruptions and resumption of therapy at a lower dose are recommended if suppression of neutrophil or thrombocyte production occurs during treatment. Therapy may also be interrupted or a lower dose may be prescribed in

response to a nonhematological adverse event (e.g., ischemic reaction, liver toxicity, or pancreatitis).

Commentary: CML is characterized by an excessive and unregulated production of white blood cells by the bone marrow resulting from a genetic abnormality involving the Bcr-Abl protein. Bcr-Abl inhibitors are initially effective but frequently cause the emergence of Bcr-Abl mutations that confer drug resistance. Because CML expresses the Bcr-Abl protein, this characteristic renders the disease potentially responsive to treatment with ponatinib.

The *T315I* mutation of Bcr-Abl currently accounts for 15% to 20% of all cases of drug resistance in CML. First-generation therapies for CML, such as imatinib mesylate (Gleevec, Novartis), and second-generation therapies for CML, such as dasatinib (Sprycel, Bristol-Myers Squibb/Otsuka), and nilotinib (Tasigna, Novartis), do not inhibit this mutated protein and thus are not effective against all forms of CML. Ponatinib was designed to inhibit a range of mutant forms of the Bcr-Abl fusion protein that are associated with drug resistance, as well as the native, unaltered form of the protein. This protein, which is derived from a genetic abnormality known as the Philadelphia chromosome, spurs the overproduction of white blood cells, a hallmark of CML.

Ponatinib appears to benefit patients who have run out of treatment options, as was shown in a phase 2 trial in which 90% of the participants had previously received at least two Bcr-Abl inhibitors (imatinib, dasatinib, or nilotinib).

Sources: www.fda.gov; www.ariad.com; *MedPage Today*, December 14, 2012

Raxibacumab Injection

Manufacturer: Human Genome Sciences, Rockville, Md.

Indication: Raxibacumab is approved to treat and prevent inhalational anthrax by neutralizing toxins produced by *Bacillus anthracis*. Anthrax is a potential biological terrorism threat because the spores are resistant to destruction, can be easily spread by release in the air, and can cause massive and irreversible tissue injury and death.

Biological Class: Raxibacumab is a human immunoglobulin G (IgG1 λ) monoclonal antibody that targets a component of the anthrax toxin.

Uniqueness of Drug: This is the first monoclonal antibody approved under the FDA's "animal efficacy rule," which allows findings from well-controlled animal studies when it is not possible or ethical to include humans. A monoclonal antibody is a protein that closely resembles a human antibody that identifies and neutralizes foreign material such as bacteria and viruses. Raxibacumab targets so-called protective antigen (PA), a component of the anthrax toxin. Blocking PA should prevent other components of the toxin from causing ill effects.

Warnings and Precautions:

Latex reactions. Caution is advised for patients with a possible history of latex sensitivity. The vial stopper contains dry natural rubber and may cause allergic reactions.

Hypersensitivity reactions. Before the injection, the patient's medical immunization history should be reviewed for possible sensitivities to vaccines or for previous vaccination-related adverse reactions to determine whether any contraindications exist. Appropriate medical treatment and supervision

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