Pharmaceutical Approval Update

Marvin M. Goldenberg, PhD, RPh, MS

Bosutinib (Bosulif) Tablets

Manufacturer: Pfizer, New York, N.Y.

Indication: Bosutinib is approved for adults with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to previous therapy with a first-generation or second-generation tyrosine kinase inhibitor (TKI).

Drug Class: The chemical name of bosutinib, a third-generation TKI, is 3-quinoLinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-, hydrate (1:1). The chemical formula is C_{26}H_{29}Cl_{2}N_{5} • H_{2}O (monohydrate), and the molecular weight is 548.46. This drug is also classified as a histone deacetylase inhibitor, which induces differentiation, cell death, or both, in tumors.

Uniqueness of Drug: Bosutinib limits cancer cell growth by inhibiting the Abl and Src signaling pathways. Other tyrosine kinases (e.g., tyrosine-protein kinase Lyn) also regulate protein behavior inside cells by attaching phosphate groups to small molecules or proteins. In the presence of the abnormal Bcr–Abl protein, Abl kinase is unregulated. Other TKIs include imatinib (Gleevec, Novartis), sunitinib (Sutent, Pfizer), nilotinib (Tasgina, Novartis), and dasatinib (Sprycel, Bristol-Myers Squibb). What is needed to treat CML is an inhibitor that works mainly on the Bcr–Abl protein mutation and not on tyrosine kinases needed for normal cells.

Warnings and Precautions:

Gastrointestinal toxicity. Diarrhea, nausea, vomiting, and abdominal pain may occur with treatment. Standards of care should be used to monitor and manage patients with anti-diarrheal drugs, antiemetic agents, and/or fluid replacement. In the single-arm phase 1/2 clinical trial, the median time to onset for all grades of diarrhea was 2 days, and the median duration per event was 1 day. Patients experiencing diarrhea had a median number of three episodes during treatment. To manage gastrointestinal (GI) toxicity, bosutinib should be withheld, given as a reduced dose, or discontinued as necessary.

Thrombocytopenia, anemia, and neutropenia may occur with bosutinib treatment. For patients who are receiving bosutinib, a complete blood count should be performed weekly for the first month, then monthly thereafter or as clinically indicated. To manage myelosuppression, bosutinib should be withheld or discontinued, or the dose can be reduced as necessary.

Hepatic toxicity. In a trial of bosutinib in combination with letrozole ( Femara, Novartis), one case was consistent with drug-induced liver injury. Hepatic injury was defined as concurrent elevations in transaminases greater than or equal to three times the upper limit of normal (ULN), total bilirubin greater than two times the ULN, and alkaline phosphatase levels below two times the ULN. The patient recovered fully after bosutinib was discontinued. This case represented one out of 1,209 patients in bosutinib clinical trials.

In the 546 patients from the safety population, the incidence of elevated alanine transaminase (ALT) levels was 17% and the incidence of elevated aspartate transaminase (AST) levels was 14%; 20% of the patients experienced an increase in either ALT or AST. Most cases of transaminase elevations occurred early in treatment. Of those patients who experienced transaminase elevations of any grade, more than 80% experienced their first event within the first 3 months.

Hepatic enzyme tests should be performed monthly for the first 3 months of treatment with bosutinib and as clinically indicated. In patients with transaminase elevations, liver enzymes should be monitored more frequently. Bosutinib should be withheld or discontinued, or the dose should be reduced, as necessary.

Fluid retention. Fluid retention has occurred with bosutinib and may be manifested as pericardial or pleural effusion, pulmonary edema, and/or peripheral edema. Patients should be monitored and managed using standards of care. Bosutinib therapy should be interrupted, discontinued, or the dose reduced, as necessary.

Embryofetal toxicity. There have not been any adequate or well-controlled studies of bosutinib in pregnant women. Bosutinib can cause fetal harm to pregnant women. It has caused embryofetal toxicities in rabbits at maternal exposures exceeding the clinical exposure at the recommended dose of 500 mg/day. Women should be advised to avoid pregnancy while being treated with bosutinib.

Dosage and Administration: The recommended dose of bosutinib is 500 mg orally, taken once daily, with food. The film-coated tablets are available in strengths of 100 mg and 500 mg.

Commentary: CML is one of the four most common types of leukemia, with more than 5,000 new cases diagnosed per year in the U.S. As many as 26,000 Americans are living with CML, a number that is expected to increase by 10-fold by the year 2040. Although strides have been made in recent years, approximately one-third of patients who received imatinib as initial therapy did not achieve optimal responses, and of those who ultimately required second-generation TKIs, approximately half did not have good outcomes. Once-daily bosutinib represents the only therapy approved on the basis of pivotal trial data that included CML patients treated with imatinib, followed by a second-generation TKI.

CML occurs mainly in patients with an abnormal Philadelphia chromosome, which results in the production of Bcr–Abl protein, a tyrosine kinase. This enzyme causes the bone marrow to produce too many white blood cells as well as immature stem cells (blasts). These blasts replace other cells made in bone marrow, including platelets and red blood cells. Bosutinib reduces cancer cell growth by inhibiting the Abl and Src signaling pathways.

The cost of the drug is estimated at $8,200 per month.

Sources: www.fda.gov; www.bosutinib.org; www.pfizerpro.com
Linaclotide (Linzess) Capsules

**Manufacturer:** Ironwood, Cambridge, U.K./Forest, St. Louis, Mo.

**Indications:** Linaclotide is approved for irritable bowel syndrome with constipation (IBS–C) in adults and for chronic idiopathic constipation (CIC) in adults.

**Drug Class:** As a guanylate cyclase-C (GC-C) agonist, linaclotide is a 14-amino acid peptide. The chemical name is l-cysteinyl-l-cysteinyl-glu-t-tyrosyl-l-cysteinyl-t-lys-yl-asparaginyl-l-prolyl-l-alanyl-l-cysteinyl-t-threonyl-glycyl-l-cysteinyl-l-tyrosine, cyclic (1-6), (2-10), (513)-tris (disulfide). The molecular formula is C_{59}H_{79}N_{15}O_{21}S_{6}, and the molecular weight is 1526.8.

**Uniqueness of Drug:** Linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C causes an increase in intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevations in intracellular cGMP stimulate secretion of chloride and bicarbonate into the intestinal lumen, mainly via activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. This action results in increased intestinal fluid and accelerated transit. In animal models, linaclotide accelerates GI transit and reduces intestinal pain. This reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which decreases the activity of pain-sensing nerves.

**Boxed Warning:** Linaclotide is contraindicated in children up to 6 years of age, and its use should be avoided in pediatric patients 6 through 17 years of age. In nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths in young juvenile mice.

**Warnings and Precautions:**

**Pediatric risk.** Linaclotide should not be given to children through 6 years of age. In nonclinical studies, deaths occurred within 24 hours in young juvenile 1- to 3-week-old mice (equivalent to humans younger than 2 years of age) following administration of one or two daily oral doses of linaclotide.

Linaclotide did not cause deaths in older juvenile mice (the equivalent of 12 to 17 years of age in humans). However, given the mortality rate in young juvenile mice and the lack of clinical safety and efficacy data for pediatric patients, linaclotide should be avoided in pediatric patients 6 through 17 years of age.

**Diarrhea.** Diarrhea was the most common adverse reaction (in 2%) with linaclotide in the pooled IBS–C and CIC double-blind, placebo-controlled trials. Rates were similar for the IBS–C and CIC populations. Patients should stop taking linaclotide if severe diarrhea occurs. Dose suspension should be considered.

**Dosage and Administration:** For patients with IBS–C, the recommended dose of linaclotide is 290 mcg taken orally once daily on an empty stomach at least 30 minutes before the first meal of the day. For patients with CIC, the recommended dose is 145 mcg taken orally once daily on an empty stomach at least 30 minutes before the first meal of the day. The capsules should be swallowed whole and should not be broken apart or chewed.

**Commentary:** The approval of linaclotide for management of CIC was established in two randomized, double-blind studies enrolling 1,272 patients who received 145 mcg or 290 mcg or placebo. After 12 weeks, treated patients experienced more complete spontaneous bowel movements than those receiving placebo. The 290-mcg dose is not approved for CIC because it was found to be no more effective than the 145-mcg dose.

The drug acts locally in the intestine with minimal systemic exposure, thereby relieving constipation. In IBS–C, it may also help ease abdominal pain.

The approximate cost to patients is $200 to $300 per month.

**Sources:** [www.linzesshcp.com](http://www.linzesshcp.com); [www.rx.com/pi/linzess_pi.pdf](http://www.rx.com/pi/linzess_pi.pdf)

Regorafenib (Stivarga) Tablets

**Manufacturer:** Bayer HealthCare, Wayne, N.J./Onyx, South San Francisco, Calif.

**Indication:** Regorafenib has been approved for patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; anti–vascular endothelial growth factor (VEGF) therapy; and an anti-epidermal growth factor receptor (EGFR) therapy (in those with the KRAS wild-type).

**Drug Class:** The chemical name of this kinase inhibitor is 4-[4-([4-chloro-3-(trifluoromethyl) phenyl] carbamoyl) amino]-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate. The molecular formula is C_{21}H_{15}ClF_{4}N_{4}O_{3} • H_{2}O. The drug’s molecular weight is 500.83.

**Uniqueness of Drug:** Regorafenib is a small-molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular function and in pathological processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. Patients must have received previous treatment with chemotherapy that included fluoropyrimidine, oxaliplatin (Eloxatin, Sanofi); irinotecan (Camptosar, Pfizer); an anti-VEGF regimen; and an anti-EGFR agent if the KRAS wild-type (normal) gene is expressed.

**Boxed Warning:** Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Hepatic function should be monitored before and during treatment. Therapy should be interrupted, reduced, or discontinued if hepatotoxicity develops, as manifested by elevated liver enzymes or hepatocellular necrosis, depending on the severity and persistence.

**Warnings and Precautions:**

**Hepatotoxicity.** Severe drug-induced liver injury with fatal outcomes occurred in 0.3% of 1,100 regorafenib-treated patients in all clinical trials. Liver biopsy results, when available, showed hepatic necrosis with lymphocyte infiltration. Liver function tests should be performed to determine ALT, AST, and bilirubin levels before therapy begins. Liver function should be monitored at least every 2 weeks during the first 2 months of treatment and monthly or more frequently as clinically indicated. Liver function tests should be monitored weekly in patients experiencing elevated hepatic enzymes until results improve to less than three times the ULN or return to baseline values.

**Hemorrhage.** In clinical trials, regorafenib was associated with an increased incidence of hemorrhage, including fatalities. Regorafenib should be permanently discontinued in patients with severe or life-threatening hemorrhage. International Normalized Ratio (INR) levels should be monitored more frequently in patients receiving warfarin.

**Dermatological toxicity.** Hand–foot skin reaction (palmar–plantar erythrodysesthesia) and rash are the most frequently observed dermatological reactions with regorafenib. Therapy continued on page 649
should be temporarily withheld and then reduced or discontin-
ued permanently, depending on the severity and persistence of
dermatological toxicity. Supportive measures for symptomatic relief should be initiated.

**Hypertension.** Elevations in blood pressure (BP) have been observed with regorafenib. Therapy should not begin until BP is controlled. BP should be monitored weekly for the first 6 weeks and then during every cycle or more frequently as clinically indicated. Regorafenib should be temporarily or permanently withheld in cases of severe or uncontrolled hypertension.

**Cardiac ischemia and infarction.** Regorafenib has been associated with an increased incidence of myocardial ischemia and myocardial infarction (MI). The drug should be withheld if new or acute cardiac ischemia or an MI occurs. Therapy should be resumed only after the event is resolved.

**Reversible posterior leukoencephalopathy syndrome (RPLS).** This syndrome has been reported with regorafenib. If the diagnosis of RPLS is confirmed with magnetic resonance imaging, regorafenib should be discontinued.

**Gastrointestinal perforation or fistula.** GI perforation and fistula have been reported in patients receiving regorafenib. Therapy should be permanently discontinued if GI perforation or fistula develops.

**Wound-healing complications.** Regorafenib should be stopped at least 2 weeks before scheduled surgery but may be resumed if wound healing is considered to be adequate. Therapy should be discontinued in patients with wound dehiscence.

**Embryofetal toxicity complications.** Regorafenib can cause fetal harm when administered to pregnant women. If the patient is using this drug during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

**Dosage and Administration:** The recommended dose of regorafenib is 160 mg orally (four 40-mg film-coated tablets) once daily for the first 21 days of each 28-day cycle. This medication is taken with food, preferably with a low-fat breakfast.

**Commentary:** According to the Centers for Disease Control and Prevention, colorectal cancer is the third most common malignancy in men and in women and the third leading cause of cancer deaths in the U.S. The National Institutes of Health estimates that 51,700 people will die from the disease in 2012.

Regorafenib can prolong survival and slow the progression of cancer in patients whose disease has progressed after treatment with currently available therapies. The drug’s approval was based primarily on a study of 760 patients. Patients receiving regorafenib plus best supportive care with such drugs as cetuximab (Erbitux, Bristol-Myers Squibb/ImClone), bevacizumab (Avastin, Genentech), or panitumumab ( Vectibix, Amgen) lived a median of 6.4 months compared with a median of 5 months in patients receiving placebo plus best supportive care. Patients treated with regorafenib plus best supportive care experienced a delay in tumor growth for a median of 2 months; patients receiving placebo plus best supportive care experienced a median delay of 1.7 months.

The wholesale cost of regorafenib is set at $9,350 for 28-day treatment course.

**Sources:** www.fda.gov; www.multivu.com; www.stivarga-
us.com