Crizotinib (Xalkori)

**Manufacturer:** Pfizer, New York, N.Y.

**Indication:** Crizotinib is designed to treat advanced non–small-cell lung cancer (NSCLC) that is positive for abnormal anaplastic lymphoma kinase (ALK).

**Drug Class:** This aminopyridine is a protein kinase inhibitor that works by competitive binding within the adenosine triphosphate (ATP)-binding pocket of target kinases. The chemical formula for crizotinib is (R)-3-[1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-[1-piperidin-4-yl]-pyridin-2-amine. The molecular weight is 450.34 daltons.

**Uniqueness of Drug:** Crizotinib, an oral, first-in-class ALK protein kinase inhibitor, was approved to treat patients with locally advanced or metastatic NSCLC whose tumor expresses the abnormal ALK gene. The drug was approved with a companion diagnostic test (the Vysis ALK Break Apart FISH Probe Kit), which can help determine whether a patient has the abnormal ALK gene (see this month’s New Devices column, page 711). Patients with this gene fusion are typically nonsmokers who do not have mutations in the epidermal growth factor receptor (EGFR) gene or in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene.

It is thought that crizotinib exerts its effects by modulating the growth, migration, and invasion of malignant cells or that it may also inhibit angiogenesis in malignant tumors.

**Warnings and Precautions:**

**Pneumonitis.** In two clinical studies, crizotinib was associated with severe, life-threatening, or fatal treatment-related pneumonitis, affecting 4 in 255 patients (1.6%). All of these cases occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms that suggest pneumonitis. Other causes of pneumonitis should be excluded. Crizotinib should be permanently discontinued if patients are found to have treatment-related pneumonitis.

**Laboratory abnormalities.** Grade 3 or 4 elevation of liver enzymes (ALT) was observed in 7% of patients in one study and in 4% of patients in another study. These elevations were generally asymptomatic and reversible upon interruption of treatment. Patients usually resumed treatment at a lower dose without recurrence; however, three patients from the first study (2%) and one patient from the second study (fewer than 1%) needed to stop treatment permanently. In both studies, concurrent elevations of alanine transaminase (ALT) levels greater than three times the upper limit of normal (ULN) and total bilirubin concentrations greater than two times the ULN without elevated alkaline phosphatase were detected in 1/255 of patients (fewer than 0.5%). Liver function tests, including ALT and total bilirubin, should be monitored once a month and as clinically indicated. More frequent repeated testing for grades 2, 3, or 4 elevations is recommended if transaminase values increase.

**Prolongation of the corrected QT interval.** Prolongation of the QT interval has been observed. Crizotinib should be avoided in patients with congenital long-QT syndrome. In patients with congestive heart failure, bradycardias, or electrolyte abnormalities or in those who are taking medications that prolong the QT interval, periodic monitoring with electrocardiograms and electrolytes should be considered.

Crizotinib should be permanently discontinued if the corrected QT (QTC) interval (grade 4) is prolonged. The drug should be withheld if grade 3 QTC prolongation occurs until values return to grade 1 or lower; at that point, a dosage of 200 mg twice daily can be resumed. If grade 3 QTC prolongation recurs, the drug should be withheld until values return to grade 1 or lower; at that point, a dosage of 250 mg once daily can be resumed. Crizotinib should be discontinued if grade 3 QTC prolongation recurs.

**ALK testing.** An FDA-approved test (the Vysis kit) is now available to detect ALK-positive NSCLC. The test is used as an aid in selecting patients for treatment with crizotinib.

**Pregnancy.** Crizotinib can cause fetal harm in pregnant women because of its mechanism of action. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dosage of 250 mg twice daily. No adequate or well-controlled studies have been conducted in pregnant women who were using crizotinib.

**Dosage and Administration:** The recommended dosage of crizotinib is 250 mg orally twice daily. Treatment should be continued as long as the patient is deriving clinical benefit from therapy. Capsules should be swallowed whole. Crizotinib may be taken with or without food. If a dose is missed, it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose. In that case, the patient should not take the missed dose. Patients should not take two doses at the same time to make up for a missed dose.

**Commentary:** Crizotinib is designed to have an effect on a genetic mutation called ALK, found in a small minority of patients with advanced lung cancer. From 1% to 7% of patients with NSCLC have the ALK gene abnormality. Crizotinib blocks certain proteins called kinases, including the protein produced by the abnormal ALK gene.

Most patients who are positive for the mutation, and who are thus likely to benefit from crizotinib, are nonsmokers with lung adenocarcinoma. The drug works quickly, and patients with symptoms of advanced lung cancer can have remarkable responses. The number of new cases of ALK-fusion NSLC is about 9,000 per year in the U.S. and about 45,000 worldwide. According to the FDA, crizotinib produced responses in 50% in one study with a median duration of response of 42 weeks. In the second study, the response rate was 61%, with a
median duration of 48 weeks. In these trials, crizotinib was given to patients who had not responded to previous chemotherapy. These are remarkable numbers. It is not known how effective this drug might be if it is given earlier in the course of treatment, perhaps as first-line therapy for recurrent or advanced lung cancer or possibly even as adjuvant therapy. However, other targeted agents that have been used to treat advanced disease with some success have not led to improved survival when they were used as an adjuvant therapy following primary surgery.

The cost of crizotinib for one year is $115,200, excluding related diagnostic tests, scans, and physician visits. Crizotinib is another in a growing list of agents that are very expensive, and it ranks close to the top for treatments that might be expected to have fairly widespread clinical use throughout the world. By comparison, the immune therapy sipuleucel-T (Provenge, Dendreon), used for advanced prostate cancer, extends life by a little over 4 months and costs $93,000 for a cycle of three treatments. The traditional defense for these expensive therapies is that the cost of drug development has skyrocketed to well over $1 billion for each successful drug that extends life by a little over 4 months and costs $93,000 for a cycle of three treatments. The traditional defense for these expensive therapies is that the cost of drug development has skyrocketed to well over $1 billion for each successful drug that is brought to market. This expense reflects the costs of basic drug research and development, the costs of clinical trials, and the fact that many drugs fail to win approval because they are either too toxic or don’t meet expectations.


Tapentadol (Nucynta) Extended-Release Tablets

Manufacturer: PriCara, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, N.J.

Indication: An extended-release (ER) form of tapentadol has been approved for the management of moderate-to-severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Tapentadol was originally approved by the FDA in 2008, and an immediate-release formulation was approved in 2009.

Drug Class: Tapentadol is a centrally acting analgesic with mu-opioid receptor agonist and norepinephrine reuptake inhibitor activity. The chemical formula is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol. The molecular weight is 221.34.

Uniqueness of Drug: The extended-release (ER) form of tapentadol is associated with fewer gastrointestinal (GI) side effects than oxycodone (OxyContin, Purdue Pharma) when it is used for pain relief in patients with osteoarthritis or chronic low back pain.

Boxed Warning:
Potential for abuse. Tapentadol ER is a Schedule II controlled substance with an abuse liability similar to that of other opioid analgesics. This fact should be considered when the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Schedule II opioid substances, which include hydromorphone (Dilaudid, Abbott), morphine, fentanyl (Duragesic, Janssen), oxymorphone (Opana, Endo), and methadone have the highest potential for abuse and risk of fatal overdose from respiratory depression. These drugs can be abused in a manner similar to that of other opioid agonists, whether legal or illicit.

Proper patient selection. The product is designed to treat patients with moderate-to-severe chronic pain who need a continuous, 24-hour opioid analgesic.

Limitations of use. Tapentadol ER is not intended for use as an as-needed analgesic or for managing acute or postoperative pain. The tablets are to be swallowed whole. Taking split, broken, chewed, dissolved, or crushed tablets could lead to rapid release and absorption of a potentially fatal dose. Patients must not consume alcoholic beverages or any medications that contain alcohol. Ingesting alcohol with tapentadol ER may result in a potentially fatal overdose of the drug.

Warnings and Precautions:
Respiratory depression. The primary risk associated with mu-opioid agonists is respiratory depression. This problem occurs more frequently in elderly or debilitated patients and in those with conditions that are accompanied by hypoxia, hypercapnia, or upper airway obstruction. Even moderate therapeutic doses may significantly decrease pulmonary ventilation in these patients.

Central nervous system depression. Tapentadol ER should be administered with caution to elderly, debilitated patients. Care should also be used when the drug is prescribed to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma.

Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with tapentadol may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma, or death may result if these drugs are taken with tapentadol ER. When combined therapy is contemplated, it may be advisable to reduce the dose of one or both agents.

Head injury. Opioid analgesics can raise cerebrospinal fluid (CSF) pressure as a result of respiratory depression with carbon dioxide retention. Therefore, tapentadol ER should not be used in patients susceptible to the effects of raised CSF pressure, such as those with a head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury because of the effects on pupillary response and consciousness. Tapentadol ER should be used with caution in patients with a head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure.

Misuse and abuse. As a Schedule II controlled substance, tapentadol ER can be abused in a manner similar to that of other legal or illicit mu-opioid agonists. All patients receiving mu-opioid agonists require careful monitoring for signs of abuse and addiction. Tapentadol ER may be abused by crushing, chewing, snorting, or injecting the product.

Overdose. Management of an overdose with tapentadol ER should focus on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishing a patent airway and instituting assisted or controlled ventilation when an overdose is suspected. Supportive measures (including
Pharmaceutical Approval Update

Tapentadol ER has not been systematically evaluated in patients with a seizure disorder. The drug should be prescribed with care if there is a history of a seizure disorder or any condition that would put the patient at risk for a seizure.

**Seizures.** Tapentadol ER has not been systematically evaluated in patients with a seizure disorder. The drug should be prescribed with care if there is a history of a seizure disorder or any condition that would put the patient at risk for a seizure.

**Serotonin syndrome.** The development of a potentially life-threatening serotonin syndrome may occur (1) with the use of serotonin–norepinephrine reuptake inhibitors (SNRIs), including tapentadol ER, particularly with the concomitant use of serotonergic drugs—such as selective serotonin reuptake inhibitors (SSRIs), SNRIs, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and triptans—and (2) with drugs that impair metabolism of serotonin (including MAO inhibitors). Serotonin syndrome may include mental status changes (agitation, hallucinations, coma), autonomic instability (tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (hyperreflexia, incoordination), or gastrointestinal symptoms (nausea, vomiting, diarrhea).

**Withdrawal.** Withdrawal symptoms may occur if tapentadol ER is discontinued abruptly. Symptoms may be reduced by tapering the dosage.

**Pregnancy Category C.** No adequate or well-controlled studies of tapentadol have been conducted in pregnant women. Tapentadol ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This drug is not recommended for women during and immediately prior to labor and delivery. Neonates whose mothers have been taking tapentadol should be monitored for respiratory depression. Tapentadol ER should not be used during breastfeeding.

**Renal and hepatic impairment.** Tapentadol ER is not recommended in patients with severe renal or hepatic impairment. Like other drugs with mu-opioid agonist activity, tapentadol ER may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

**Dosage and Administration:** The tablets should be swallowed whole and should not be split, broken, chewed, dissolved, or crushed.

The recommended maintenance dose is 100 mg to 250 mg twice daily, taken approximately every 12 hours. The maximum 24-hour dose is 500 mg. Patients should not exceed a total daily dose of 500 mg. The dosing regimen should be individualized according to any risk factors for abuse or addiction, the patient's age, general condition, and medical status; opioid exposure and opioid tolerance; daily dose potency and kind of analgesic the patient has been taking; and the balance between pain management and adverse reactions. During periods of changing analgesic requirements, including initial titration, frequent contact with the patient should be maintained.

**Commentary:** Tapentadol ER tablets are indicated for adults with moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The ER formulation may result in better long-term compliance and longer pain relief than oxycodone controlled-release (CR) in patients with moderate-to-severe chronic low back or osteoarthritis pain. These results were supported in a post hoc analysis of a phase 3 randomized, open-label, 1-year safety study, with tapentadol ER 100 to 250 mg twice daily in 894 patients. The drug demonstrated pain relief similar to that of oxycodone CR 20 to 50 mg twice daily in 223 patients, with a lower incidence of treatment-emergent adverse events.

Tapentadol ER can be abused in a manner similar to other legal or illegal opioid agonists. Schedule II opioid substances (e.g., hydromorphone, morphine, oxycodone, fentanyl, oxymorphone, and methadone) have the highest potential for abuse and a risk of a fatal overdose because of the possibility of respiratory depression.

Source: www.nucynta.com

**Eculizumab (Soliris)**

**Manufacturer:** Alexion, Cheshire, Conn.

**Indication:** Previously, eculizumab was approved for patients with paroxysmal nocturnal hemoglobinuria (PNH), a life-threatening disease characterized by the excessive destruction of red blood cells (hemolysis). Eculizumab is now also indicated for patients with atypical hemolytic uremic syndrome (aHUS), a rare, life-threatening genetic blood disease that can progressively damage vital organs, leading to stroke, heart attack, kidney failure and death. Eculizumab is the first therapy approved for the treatment of aHUS. It works by inhibiting complement-mediated thrombotic microangiopathy. The disease affects children disproportionately.

**Drug Class:** A first-in-class terminal complement inhibitor, eculizumab is a recombinant humanized monoclonal immunoglobulin (IgG) antibody that binds to the complement protein C5, inhibiting its cleavage by the C5 convertase and prevents the generation of the terminal complement complex C5b-9.

**Uniqueness of Drug:** Eculizumab targets and blocks the terminal complement cascade, a normal part of the immune system that, when activated inappropriately, plays a role in serious diseases like PNH and aHUS. Eculizumab is produced by murine myeloma cell culture and is composed of two 448 amino acid heavy chains and two amino acid light chains. Its molecular weight is about 148 daltons.

**Boxed Warning:** Life-threatening and fatal meningococcal infections have occurred in patients. Meningococcal infection may become rapidly life-threatening if it is not recognized and treated early. The most current Advisory Committee on Immunization Practices (ACIP) recommendations are for meningococcal vaccination in patients with complement deficiencies. Patients should receive a meningococcal vaccine at least 2 weeks before receiving the first dose of eculizumab unless the risks of delaying therapy outweigh the risk of developing a meningococcal infection. Patients should be monitored for early signs of meningococcal infections and should be evaluated immediately if infection is suspected.

Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Prescribers must enroll in the program.

**Warnings and Precautions:** Caution should be exercised...
when eculizumab is prescribed to patients with a systemic infection. Eculizumab increases the number of red blood cells. All patients who discontinue eculizumab therapy should be monitored for signs and symptoms of intravascular hemolysis, including evaluation of serum lactate dehydrogenase levels.

**Dosage and Administration:** For adults, the intravenous (IV) dose is 600 mg every 7 days for the first 4 weeks, 900 mg 7 days later for the fifth dose, and 900 mg every 14 days thereafter.

A meningococcal vaccine should be administered at least 2 weeks before patients begin eculizumab therapy, and re-vaccination should be scheduled according to current medical guidelines. The IV infusion is given over a period of 35 minutes via a gravity feed, a syringe-type pump, or an infusion pump.

The product should be diluted to a final administration concentration of 5 mg/mL by adding the appropriate amount of sodium chloride 0.9% or 0.45%, dextrose 5% in water, or Ringer’s lactate injection. The infusion bag should be gently inverted to ensure thorough mixing. The admixture is not to be shaken. Before administration, the admixture should be allowed to adjust to room temperature. Microwaving should be avoided, and no heat source other than ambient air temperature should be used. If an adverse reaction occurs during administration, the infusion should be slowed or stopped as needed. The total infusion time should not exceed 2 hours. The product should be visually inspected for particulate matter and discoloration.

**Commentary:** The FDA granted an accelerated approval of eculizumab for children and adults with aHUS.

Because eculizumab affects the immune system, it may increase the risk of a serious infection such as meningitis. Meningococcal disease resulting from any serogroup may occur with eculizumab. To reduce the risk of infection, all patients should be vaccinated against meningitis at least 2 weeks before they receive eculizumab, and they should be re-vaccinated according to current medical guidelines. Tetravalent vaccines against serotypes A, C, Y, and W135, preferably conjugated vaccines, are recommended. However, vaccination might not be sufficient to prevent meningococcal infection. All patients should be monitored for early signs of meningococcal infection and evaluated immediately if infection is suspected. Antibiotics should be used if necessary. Patients should be informed about these signs and symptoms and about the need to seek medical care immediately.

According to Financial Times (October 10, 2011), eculizumab is the world’s most expensive medication, approaching $500,000 per year. Alexion was reported to have raised the price by 2.9%, from $5,376 to $5,532 per 300-mg vial.

**Sources:** www.drugs.com/ppa/eculizumab.html; http://blackboxrx.com/app/display.php?id=390; www.ft.com/cms/s/2/d031ed94-f364-11e0-b98c-00144feab49a.html#axzz1bi8b7dV9