Blinatumomab (Blincyto)

**Manufacturer:** Onyx Pharmaceuticals (an Amgen subsidiary), South San Francisco, California

**Date of Approval:** December 3, 2014

**Indication:** Blincyto is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication was granted under accelerated approval; continued approval may be contingent upon verification of clinical benefit in subsequent trials. Blincyto is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation.

**Drug Class:** Monoclonal antibody

**Uniqueness of Drug:** Blinatumomab binds to the surface antigen CD19 on B cells and CD3 on T cells as a bispecific CD19-directed CD3 T-cell engager. Blinatumomab then activates endogenous T cells by connecting the T-cell receptor complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, up-regulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

**Warnings and Precautions:**

**Cytokine release syndrome (CRS).** Potentially life-threatening or fatal CRS occurred in patients receiving blinatumomab. Infusion reactions have also occurred during blinatumomab administration and may be clinically indistinguishable from manifestations of CRS. Serious adverse events may be associated with CRS, and patients should be closely monitored for signs or symptoms of these events. Management of these events may require either temporary interruption or discontinuation of blinatumomab.

**Neurological toxicities.** Monitor patients receiving blinatumomab for signs and symptoms of neurological toxicities, and interrupt or discontinue blinatumomab as recommended.

**Infections.** As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with blinatumomab. Monitor patients for signs and symptoms of infection and treat appropriately.

**Tumor lysis syndrome (TLS).** This potentially life-threatening or fatal problem has been observed in patients receiving blinatumomab. Appropriate prophylactic measures, including nontoxic cytoreduction before treatment and hydration during treatment, should be used to prevent TLS during blinatumomab therapy. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of blinatumomab.

**Neutropenia and febrile neutropenia.** Cases, some of them life-threatening, have been observed in patients receiving blinatumomab. Monitor laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during blinatumomab infusion. Interrupt blinatumomab if prolonged neutropenia occurs.

**Effects on the ability to drive and use machines.** Due to the potential for neurological events, including seizures, patients receiving blinatumomab are at risk for loss of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, while blinatumomab is being administered.

**Elevated liver enzymes.** Monitor alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and total blood bilirubin prior to the start of and during blinatumomab treatment. Interrupt blinatumomab if the transaminases rise to greater than five times the upper limit of normal or if bilirubin rises to more than three times the upper limit of normal.

**Leukoencephalopathy.** Cranial magnetic resonance imaging changes showing leukoencephalopathy have been observed in patients receiving blinatumomab, especially those who have undergone prior treatment with cranial irradiation and antileukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

**Preparation and administration errors.** Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including underdose and overdose), which have occurred with blinatumomab treatment.

**Dosage and Administration:** A single cycle of treatment of blinatumomab consists of four weeks of continuous intravenous (IV) infusion followed by a two-week treatment-free interval. For patients who weigh at least 45 kg, blinatumomab should be administered at 9 mcg per day on days 1 to 7 and at 28 mcg per day on days 8 to 28 in cycle 1. For subsequent cycles, blinatumomab should be administered at 28 mcg per day on days 1 to 28. Allow at least two treatment-free weeks between cycles of blinatumomab.

Patients should be premedicated with dexamethasone 20 mg IV one hour prior to the first dose of blinatumomab of each cycle; prior to a step dose (such as cycle 1, day 8); or when restarting an infusion after an interruption of four or more hours. Administer blinatumomab as a continuous IV infusion at a constant flow rate using an infusion pump. It is important not to flush the infusion line, especially when changing infusion bags, which may result in the delivery of too much medication.

**Commentary:** Blincyto is part of a new class of medications called immunotherapies, which are designed to utilize a patient’s immune system to fight diseases. This novel medication was approved for an uncommon form of ALL under multiple FDA designations. FDA granted Blincyto priority review, orphan product designation, and breakthrough therapy designation, allowing its approval more than five months ahead of schedule. It was also reviewed under the FDA’s acceler-
Gardasil 9 is indicated in females 9 through 26 years of age for prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by human papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Condyloma acuminata (genital warts) caused by HPV types 6 and 11
- The following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
  - Cervical intraepithelial neoplasia (CIN) grade 1 and grade 2/3
  - Cervical adenocarcinoma in situ (AIS)
  - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
  - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Gardasil 9 is indicated in boys 9 through 15 years of age for prevention of the following diseases:
  - Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
  - Condyloma acuminata caused by HPV types 6 and 11
  - AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

The use and effectiveness of Gardasil 9 has the following limitations:

- Gardasil 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.
- Recipients of Gardasil 9 should not discontinue anal cancer screening if a health care provider has recommended such screening.
- Gardasil 9 has not been shown to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.
- Gardasil 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58.
- Gardasil 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.
- Not all vulvar, vaginal, and anal cancers are caused by HPV, and Gardasil 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Gardasil 9 does not protect against genital diseases not caused by HPV.

Drug Class: Vaccine

Uniqueness of Drug: Gardasil 9 is thought to mediate humoral immune responses against anogenital diseases related to the vaccine HPV types in human beings, although the exact mechanism of protection is unknown.

Warnings and Precautions:

Syncope. Because vaccines may cause syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

Managing allergic reactions. Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of Gardasil 9.

Dosage and Administration: Administer Gardasil 9 intramuscularly as a 0.5-mL dose at the following schedule: 0, 2, and 6 months.

Commentary: HPV can progress to various forms of cancer. Gardasil was initially approved in 2006 as an important tool for female cervical cancer prevention related to four different types of HPV. Gardasil 9 expands the vaccine’s indication to cover nine HPV types. This vaccine now has the potential to prevent approximately 90% of cervical, vulvar, vaginal, and anal cancers.


Hydrocodone Bitartrate Extended Release (Hysingla ER)

Manufacturer: Purdue Pharma LP, Stamford, Connecticut

Date of Approval: November 20, 2014

Indication: Hysingla ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Use of Hysingla ER has the following limitations:

- Hysingla ER should be reserved for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Hysingla ER is not indicated as an as-needed analgesic.

Hysingla ER is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus and gastrointestinal (GI) obstruction
- Hypersensitivity to any component of Hysingla ER or the active ingredient, hydrocodone bitartrate
Drug Class: Opioid agonist

Uniqueness of Drug: Hydrocodone is a semisynthetic opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and spinal cord, which are coupled to G-protein complexes and modulate synaptic transmission through adenylate cyclase. The pharmacological effects of hydrocodone, including analgesia, euphoria, respiratory depression, and physiological dependence, are believed to be primarily mediated via mu-opioid receptors.

Warnings and Precautions:

Addiction, abuse, and misuse. Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing Hysingla ER, and monitor all patients receiving the drug for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of the medication for the proper management of pain in any given patient.

Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug. Contact the appropriate state professional licensing board or state controlled-substances authority for information on how to prevent and detect abuse or diversion of this product.

Life-threatening respiratory depression. If not immediately recognized and treated, respiratory depression from opioid use may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of the drug, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with the medication and following dose increases. To reduce the risk of respiratory depression, proper dosing and titration of the drug are essential. Overestimating the dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

Neonatal opioid withdrawal syndrome. Prolonged use of Hysingla ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Interactions with central nervous system (CNS) depressants. When considering the use of Hysingla ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed. Additionally, evaluate the patient’s use of alcohol or illicit drugs that cause CNS depression. If the decision to begin Hysingla ER is made, start with a lower dose than usual (i.e., 20% to 30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant.

Use in elderly, cachectic, and debilitated patients. Life-threatening respiratory depression is more likely to occur in these patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Hysingla ER and when giving it concomitantly with other drugs that depress respiration.

Use in patients with chronic pulmonary disease. Monitor patients for respiratory depression if they have significant chronic obstructive pulmonary disease or cor pulmonale; a substantially decreased respiratory reserve; hypoxia; hypercapnia; or pre-existing respiratory depression, particularly when initiating therapy and titrating with Hysingla ER. In these patients, even usual therapeutic doses of the drug may decrease respiratory drive to the point of apnea. Consider the use of alternative nonopioid analgesics in these patients if possible.

Use in patients with head injury and increased intracranial pressure. Closely monitor patients who may be susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury. Avoid the use of the medication in patients with impaired consciousness or coma.

Hypotensive effect. Hysingla ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents that compromise vasomotor tone. Monitor these patients for signs of hypotension after initiating or titrating the dose of the drug. In patients with circulatory shock, Hysingla ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of the medication in patients with circulatory shock.

GI obstruction, dysphagia, and choking. Instruct patients not to presoak, lick, or otherwise wet Hysingla ER tablets prior to placing them in the mouth. Patients should take one tablet at a time with enough water to ensure complete swallowing immediately after placing the tablet in the mouth. Patients with underlying GI disorders, such as esophageal cancer or colon cancer with a small GI lumen, are at greater risk of these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small GI lumen.

Decreased bowel motility. Hysingla ER is contraindicated in patients with known or suspected GI obstruction, including paralytic ileus. Monitor for decreased bowel motility in postoperative patients receiving opioids. Monitor patients with biliary tract disease, including acute pancreatitis.

Cytochrome P450 CYP3A4 inhibitors and inducers. The CYP3A4 isoenzyme plays a major role in the metabolism of Hysingla ER. Drugs that alter CYP3A4 activity may cause changes in hydrocodone clearance, which could lead to changes in hydrocodone plasma concentrations. If coadministration continued on page 122
is necessary, caution is advised when initiating Hysingla ER treatment in patients currently taking or discontinuing CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Driving and operating machinery. Hysingla ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of the drug and know how they will react to the medication.

Interaction with mixed agonist/antagonist opioid analgesics. Avoid the use of mixed agonist/antagonist analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Hysingla ER. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

QTc interval prolongation. This effect has been observed with Hysingla ER following daily doses of 160 mg. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing the drug to patients who have congestive heart failure, bradyarrhythmias, or electrolyte abnormalities or who are taking medications known to prolong the QTc interval. The medication should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose of the drug by 33% to 50% or changing to an alternate analgesic.

Dosage and Administration: Hysingla ER should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Initiate the dosing regimen for each patient individually, taking into account the patient’s prior analgesic treatment experience and risk factors for addiction, abuse, and misuse. Hysingla ER is administered orally every 24 hours and must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing the tablet in the mouth. The typical initiation dosage is 20 mg orally every 24 hours in patients for whom this is the first opioid analgesic. Dose titration may occur every three to five days.

Commentary: With numerous pain medications readily available, the abuse potential among patients receiving opioids has risen dramatically over the years. In 2013, the FDA approved a draft guidance to aid manufacturers when developing opioid formulations with abuse-deterrent properties. Approval for Hysingla ER will give prescribers another option to manage a patient’s severe pain while potentially reducing hydrocodone abuse. As the only approved 24-hour formulation for extended-release hydrocodone, the most frequently abused opioid, Hysingla ER may become a safer alternative to other therapies. Hysingla ER is expected to be available this month.

Sources: www.fda.gov, www.streetinsider.com, and Hysingla ER prescribing information

Pharmaceutical Approval Update

continued from page 108