Azacitidine for Injection (Vidaza), Intravenous or Subcutaneous

**Manufacturer:** Pharmion Corporation, Boulder, Colo.

**Drug Class:** Azacitidine for injection is a pyrimidine nucleoside analogue of cytidine. The drug’s formula is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one.

**Uniqueness of Drug:** Azacitidine, an antineoplastic agent, utilizes a dual mechanism of action, causing the hypomethylation of DNA and exerting direct cytotoxicity in abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal gene function to genes controlling cellular division and differentiation (the genes presumed to be abnormal or nonfunctional in myelodysplastic syndromes). Cytotoxic effects cause the death of rapidly dividing abnormal cells. Azacitidine is not strongly active in nonproliferating cells; thus, toxicity is limited to that resulting from affected tissues.

**Indication:** Azacitidine was approved as an injectable suspension in 2004 for the treatment of myelodysplastic syndrome subtypes, including refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions); refractory anemia with excess blasts (RAEB); refractory anemia with excess blasts in transformation (RAEB-t); and chronic myelomonocytic leukemia (CML). These syndromes result in underproduction of healthy blood cells.

**Medically Accepted Off-Label Uses:** This category represents only those indications that have been submitted to the American Hospital Formulary Service: Drug Information (AHFS DI) via a formal application process. A medically accepted off-label use of azacitidine is for acute myelogenous leukemia (AML) with multilineage dysplasia (previously RAEB-t).

**Dose regimen:** Azacitidine 75 mg/m² is administered as a subcutaneous (SQ) injection on days one to seven on an every-28-day cycle.

**Strength of evidence (study endpoints):** Level 3; low quality (overall).

**Grade of recommendation (final composite ratings):** B-2 for AML (previously RAEB-t) (overall survival). This was determined to be a “Reasonable Choice” (i.e., treatment option); it is reasonable to use the drug under certain conditions (e.g., patient subgroups); can be useful, effective, and beneficial and is probably recommended or indicated.

**Disclosure information:** AHFS DI committee members have disclosed no conflict of interest for this particular matter review. A consultant who provided expert commentary disclosed consultant activities with Pharmion and Celgene, participated in speaker’s bureau activities with MGI and Celgene, and had equity interests in Celgene; however, the consultant did not participate in or vote on the final determination.

Another off-label use (as determined by AHFS DI) is for untreated AML in elderly patients (older than 60 years of age) who are not considered eligible to receive conventional induction therapy, as defined by a poor performance status or evidence of a clinically important comorbidity.

**Dose regimen:** Azacitidine 75 mg/m² is administered as a subcutaneous (SQ) injection on days one to seven on an every-28-day cycle.

**Endpoints:** Objective response rate (ORR) and overall survival.

**Grade of recommendation:** B-3 for elderly patients with AML (ORR and survival)

**Disclosure information:** AHFS DI committee members have disclosed no conflict of interest for this particular matter review. A consultant who provided expert commentary disclosed consultant activities with Pharmion and Celgene, participated in speaker’s bureau activities with MGI and Celgene, and had equity interests in Celgene; however, the consultant did not participate or vote on the final determination.

Sources: www.vidaza.com; www.ashp.org/ahfs/off-label-uses/azacitidine.pdf

Lubiprostone (Amitiza)

**Manufacturer:** Sucampo Pharmaceuticals, Inc., Division of Takeda, Deerfield, Ill.

**Indications:** Irritable bowel syndrome with constipation (new). Lubiprostone is indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women 18 years of age and older. IBS-C is also called constipation-predominant irritable bowel syndrome.

**Chronic idiopathic constipation (previously FDA-approved).** Lubiprostone was approved for the treatment of chronic idiopathic constipation in adults in January 2006.

**Drug Class:** A locally acting chloride channel activator, lubiprostone triggers type-2 chloride channels (CIC-2), a normal constituent of the luminal membrane of the human intestine that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium serum concentrations. By increasing intestinal fluid secretion, lubiprostone increases intestinal motility, which facilitates the passage of stool and alleviates symptoms associated with IBS-C in women and with chronic idiopathic constipation in men and women.

**Uniqueness of Drug:** Compared with current therapies on the market, lubiprostone locally activates specific chloride channels (CIC-2) in the lining of the small intestines after oral administration, thereby increasing intestinal fluids and softening bowel movements.

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**Warnings and Precautions:**

**Pregnancy.** The safety of lubiprostone in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone had the potential to cause fetal loss. This agent should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. Women who could become pregnant should have a negative pregnancy test before beginning therapy with lubiprostone and should be capable of complying with effective contraceptive measures.

**Nausea.** Patients taking lubiprostone may experience nausea. If this occurs, concomitant administration of food may reduce symptoms.

**Diarrhea.** Lubiprostone should not be prescribed for patients with severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment, and they should be instructed to inform their physician if severe diarrhea occurs.

**Dyspnea.** In clinical trials, dyspnea was reported in 2.5% of the treated patients with chronic idiopathic constipation and in 0.4% of the treated patients with IBS-C. Although adverse events were not classified as serious, some patients discontinued treatment because of dyspnea. Dyspnea has usually been described as a sensation of chest tightness and difficulty in taking in a breath, generally with an acute onset within 30 to 60 minutes after taking the first dose. There have been post-marketing reports of dyspnea when lubiprostone was used at a dose of 24 mcg. Symptoms of dyspnea generally resolved within a few hours after patients took the dose, but recurrence has been frequently reported with subsequent doses of lubiprostone.

**Bowel obstruction:** In patients with symptoms suggesting mechanical gastrointestinal obstruction, the physician should perform a thorough evaluation to confirm the absence of such an obstruction before initiating therapy with lubiprostone.

**Dosage and Administration:** Lubiprostone should be taken twice daily orally with food and water. Physicians and patients should periodically assess the need for continued therapy.

**Irritable bowel syndrome with constipation.** The recommended dose is 8 mcg taken twice daily orally with food and water.

**Chronic idiopathic constipation.** The recommended dose is 24 mcg taken twice daily orally with food and water.

**Commentary:** IBS is a chronic, recurrent disorder characterized by the multiple symptoms of abdominal pain and discomfort, bloating, and extreme changes of bowel habits such as constipation, diarrhea, or both. IBS is considered to be one of the most common gastrointestinal (GI) disorders. Approximately 30 million people in North America meet the diagnostic criteria for IBS. According to the American Gastroenterological Association, the cause of IBS is unknown, although lifestyle factors (including diet) and psychological stress may play a role.

IBS affects 1 in 10 adults in the U.S., making it one of the most common ailments diagnosed by physicians. Both IBS (especially IBS-C) and chronic idiopathic constipation are common GI conditions that occur more frequently in women; 60% to 70% of patients are women.

IBS is the most common diagnosis by gastroenterologists and causes a great deal of discomfort and distress for patients. IBS is not life-threatening, but it can significantly interfere with daily activities and can reduce the patient’s quality of life.

Although the approval of lubiprostone offers a medication that can provide overall symptom relief for the millions of adult women in the U.S., physicians must be cautious, because the drug has not been studied in pregnant women. It should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

**Sources:** www.amitiza.com; www.drugs.com/nda/lubiprostone_05041.html; www.womenshealthcareforum.com/IBS.cfm