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Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class: Antiemetic Agents

Overview:

Dolasetron, granisetron, ondansetron, and palonosetron are the 5-HT₃ receptor antagonists available in the US. These agents became available in the early 1990s. The development of this class of medications greatly enhanced the prevention of chemotherapy-induced nausea and vomiting. The 5-HT₃ receptor antagonists selectively block type 3 serotonin (5-HT₃) receptors that are located in the chemoreceptor trigger zone and at vagal nerve terminals in the intestines. Because serotonin is a major neurotransmitter involved in emesis, blocking the serotonin receptor, 5-HT₃, inhibits the ability of serotonin to activate vomiting centers. In May 2003, a selective substance P/neurokinin 1 (NK₁) receptor antagonist, aprepitant, was introduced for the treatment of chemotherapy-induced nausea and vomiting. The NK₁ antagonist blocks receptors present in the brain stem (medulla) centers that control the emetic reflex. Due to additive mechanisms, the NK₁ antagonist enhanced protection against both acute and delayed phases of chemotherapy-induced nausea and vomiting in combination with a 5HT₃-receptor antagonist and a corticosteroid. In June 2006, aprepitant was FDA-approved for the prevention of postoperative nausea and vomiting (PONV).

Selective 5-HT₃ receptor antagonists have been widely used for the control of nausea/vomiting caused by chemotherapy, radiation therapy, or surgery. Dolasetron is only indicated for post-operative and chemotherapy induced nausea/vomiting. It is not indicated for radiation- induced nausea/vomiting. On the other hand, ondansetron and granisetron are indicated for nausea/vomiting caused by chemotherapy, radiation therapy, or surgery. Palonosetron is the first drug in this class approved for the prevention of delayed nausea and vomiting associated with chemotherapy. In February 2008, Palonosetron was also approved for the prevention of nausea and vomiting for up to 24 hours following surgery. At this time, Aloxi[®] (palonosetron) is only available in an injectable formulation. The 5-HT₃ antagonists are generally well tolerated with mild adverse events; however, dolasetron increases PR, QT and QRS intervals significantly more than the other agents in the class. Based on available clinical evidence and when administered at equivalent doses, the 5-HT₃ antagonists have demonstrated equivalent efficacy and similar safety. Moreover, at equivalent doses, oral agents are equally effective and are as safe as intravenous agents. In most settings, oral agents are less costly and more convenient to administer. Ondansetron disintegrating tablets (Zofran ODT[®]) provide an easy administration option for patients who have difficulty swallowing tablets. The first transdermal patch, Sancuso[®] (granisetron), recently received FDA approval for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to five consecutive days

duration. It is important to note that higher doses of 5-HT₃ antagonists are not more efficacious than the doses recommended by manufacturers.

Aprepitant is the first and only agent in the class of NK₁ receptor antagonists. In combination with a corticosteroid and a 5-HT₃ antagonist, aprepitant is indicated for delayed nausea and vomiting induced by highly emetogenic cancer chemotherapy including platinum-based chemotherapy. Aprepitant has recently gained approval for use 1) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in combination with other antiemetic agents, and 2) for the prevention of postoperative nausea and vomiting (PONV) without other antiemetic agents. Fosaprepitant dimeglumine, a prodrug of aprepitant, is now approved and available in an injectable formulation that may be given in place of the oral product 30 minutes prior to chemotherapy on Day 1 of the chemotherapy induced nausea and vomiting regimen.

Dronabinol (Marinol), a synthetic cannabinoid, is FDA-approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics. With mildly or moderately emetogenic chemotherapy, dronabinol is more effective than placebo and equivalent or superior to oral prochlorperazine. Head to head comparisons with 5-HT₃ antagonists are limited. The American Society of Clinical Oncology (ASCO) currently recommends a regimen consisting of a 5-HT₃ receptor antagonist, dexamethasone, and aprepitant to prevent chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic regimens. Antiemetic agents which are less efficacious and generally associated with more frequent adverse effects (including cannabinoids, metoclopramide, butyrophenones, and phenothiazines) are not considered by ASCO to be appropriate first-line antiemetics for any group of patients receiving chemotherapy of high emetic risk.

Generic Name	Brand Name	Manufacturer	Generic Available
Aprepitant	Emend [®]	Merck	N
Dolasetron	Anzemet [®]	Aventis	N
Dronabinol	Marinol [®]	Solvay	Y
Fosaprepitant dimeglumine	Emend [®] Injection	Merck	N
Granisetron	Kytril [®] , Sancuso [®]	Roche, ProStrakan	Y (Kytril only)
Ondansetron	Zofran [®] , Zofran ODT [®]	GlaxoSmithKline	Y
Palonosetron	Aloxi [®]	MGI Pharma Inc.	N

Summary:

5-HT₃ antagonists have been widely used for the control of nausea/vomiting caused by chemotherapy, radiation therapy or surgery. Dolasetron, granisetron, ondansetron and



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palonosetron are the 5-HT₃ antagonists available in the United States. 5-HT₃ antagonists are generally well tolerated with mild adverse events. However, dolasetron seems to increase PR, QT and QRS intervals more significantly than the other agents in the class.

Based on clinical evidence, the 5-HT₃ antagonists at equivalent doses demonstrated equivalent efficacy and similar safety. In most settings, oral agents are equivalent to injections. Furthermore, higher doses of 5-HT₃ antagonists are not more efficacious than the doses recommended by the manufacturers. Selection of 5-HT₃ agents for inclusion on the preferred drug list should take into consideration efficacy, safety, and cost-effectiveness. One oral agent with a monthly tablet limit could facilitate the appropriate use of the 5-HT₃ antagonists. Aprepitant is first in a new therapeutic class of highly selective substance P/neurokinin 1 (NK₁) receptor antagonists. In combination with a corticosteroid and a 5HT₃ antagonist, aprepitant is indicated for delayed nausea and vomiting induced by platinum based chemotherapy. Because of its unique place in therapy, a prior authorization program is warranted to ensure aprepitant is being used appropriately. Dronabinol is a synthetic cannabinoid that is FDA approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics. As per ASCO, this agent should be reserved for patients unable to tolerate or are refractory to first-line agents.