

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 of 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 the receptors present in the brain stem (medulla) centers that control the emetic reflex. Because of the additive mechanisms, the NK₁ antagonist enhanced the 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 received FDA approval 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 (available in injection form only). In February 2008, Palonosetron received approval for the prevention of nausea and vomiting for up to 24 hours following surgery. 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. Additionally, higher doses of 5-HT₃ antagonists are not more efficacious than the doses recommended by the 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.

Generic Name	Brand Name	Manufacturer	Generic Available
Aprepitant	Emend [®]	Merck	N
Dolasetron	Anzemet [®]	Aventis	N
Fosaprepitant dimeglumine	Emend [®]	Merck	N

Granisetron	Kytril [®] , Granisol [™]	Roche	Y
Ondansetron	Zofran [®] , Zofran ODT [®]	GlaxoSmithKline	Y
Palonosetron	Aloxi [®]	MGI Pharma Inc.	N

Summary:

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. Also of note, ondansetron 4-, 8-, 16-, and 24-mg orally disintegrating tablets, ondansetron 4 mg/5-mL oral solution, ondansetron 4-, 8-, 16-, and 24-mg oral tablets, ondansetron 2-mg/mL injection, and 0.64-mg/mL solution for infusion have been approved. However, the 16-mg orally disintegrating tablets and the 16-mg tablets are not yet commercially available. Additionally, granisetron 1-mg/mL injection, 1-mg tablets, and 1mg/5mL oral solution (Granisol[™]) have been approved and are available. NK₁ antagonist has a unique place in therapy. A prior authorization program can ensure aprepitant is being used appropriately.