Therapeutic Class Overview
Neurokinin-1 (NK1) Receptor Antagonists and Combinations

Therapeutic Class Overview/Summary:
This review will focus on miscellaneous antiemetics, which includes doxylamine succinate/pyridoxine hydrochloride (Diclegis®) as well as the neurokin-1 (NK_1) receptor antagonists/combinations. NK_1 antagonists are all Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV).[1-5] Single-entity NK_1 antagonists include: aprepitant (Emend®), its prodrug fosaprepitant dimeglumine (Emend®), and rolapitant hydrochloride (Varubi®). There is a single NK_1 antagonist combination product currently available, netupitant/palonosetron (Akynzeo®). With this combination, netupitant, the NK_1 antagonist is co-formulated with palonosetron, a serotonin type-3 (5-HT_3) receptor antagonist. In addition to CINV, aprepitant is FDA-approved for the prevention of post-operative nausea and vomiting in adults.[1-4] Differences in anti-emetic effect for the acute and delayed phases of CINV exist between NK_1 antagonists and are summarized in Table 2. Doxylamine/pyridoxine is FDA-approved for the treatment of nausea and vomiting of pregnancy.[5]

As the pathophysiology of CINV is not completely understood, the exact mechanisms by which NK_1 antagonists exert there antiemetic effects are not known. NK_1 is a broadly distributed receptor located in both the central and peripheral nervous systems. One proposed mechanism of NK_1 antagonists is by depressing the substance P mediated response in the central nevous system by blocking activation of NK_1 in areas of the brain responsible for chemoreception. Decreased activation of NK_1 by substance P reduces the emetic reflex. A second proposed mechanism is the blockade of peripheral NK_1 receptors located on the vagal terminals of the gut. It is hypothesized that peripheral blockade may decrease the intensity of the signal transmitted to the central nervous system, thus decreasing the overall emetic reflex.[1-4,6,7] Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[5,8,9]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Aprepitant (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of CINV associated with initial and repeat courses of MEC, Prevention of PONV	Capsule: 40 mg 80 mg 125 mg Capsule, Dose Pack: 125 and 80 mg Oral Suspension: 125 mg/5 mL	-
Fosaprepitant dimeglumine (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC	Vial: 150 mg	-
Rolapitant hydrochloride	Prevention of delayed CINV	Tablet:	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Varubi®)	associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC and prevention of delayed CINV associated with combination of anthracycline and cyclophosphamide	90 mg	
Doxylamine succinate/pyridoxine hydrochloride (Diclegis®)	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management	Delayed-release tablet: 10 mg/10 mg	-
Netupitant/palonosetron (Akynzeo®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of acute and delayed CINV associated with initial and repeat courses of cancer chemotherapy not considered highly emetogenic	Capsule: 300/0.5 mg	-

Other abbreviations: CINV=chemotherapy-induced nausea and vomiting, HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy, PONV=post-operative nausea and vomiting

Evidence-based Medicine

- The safety and efficacy of the miscellaneous antiemetics have been evaluated in several clinical trials for their FDA-approved indications.[15-51] Aprepitant, being an older, more established agent has had more extensive review. Results of these trials are similar to those used by the FDA for approval.[19-36] There are currently no clinical trials that compare NK_1 antagonists to one-another.
- The approval of rolapitant (Varubi®) was based on the efficacy and safety in preventing CINV in patients receiving anthracycline combination therapy, MEC, or HEC with a cisplatin-based regimen in three clinical trials. The primary endpoint in both HEC studies was complete response (CR) in the delayed phase (defined as 25 to 120 hours post administration of chemotherapy) of CINV. Results of the showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group in HEC-1: (192 [73%] compared to 153 [58%]; P=0.0006). However, in HEC-2, this was statistically significant: (rolapitant [70%] compared to placebo control group [62%]; P=0.0426).[39,40] In the third trial, the antiemetic effect of rolapitant was evaluated in MEC. The primary endpoint of CR in the delayed phase of CINV showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group: (475 [71%] compared to 410 [62%]; P=0.0002).[39,41]
- The approval of netupitant/palonosetron (Akynzeo®) was based on the efficacy and safety in preventing CINV in patients receiving MEC or HEC. Both trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone. CR in the delayed phase was statically significant in HEC and MEC for patients who received netupitant/palonosetron (P=0.032 and P=0.01, respectively).[42,43]
- FDA-approval of doxylamine succinate/pyridoxine hydrochloride (Diclegis®) was based on a single double-blind, randomized, multi-center, placebo-controlled study that evaluated 298 pregnant adult women with nausea and vomiting in the gestational age range of 7 to 14 weeks. Patients were randomized to 14 days of placebo or doxylamine/pyridoxine (two to four tablets daily). Mean change from baseline was -4.8 points in the symptom domain (Pregnancy Unique-Quantification of Emesis) score at day 15 in the doxylamine/pyridoxine group compared to -3.9 points in the placebo group (P=0.006). For the Quality of Life domain, mean change from baseline was 2.8 points at day 15 in the

doxylamine/pyridoxine group compared to -1.8 points in the placebo group (P=0.005).[50] A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine/pyridoxine. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively).[51]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - It is recommended that antiemetic therapy be initiated before the administration of chemotherapy and then continued throughout the period when delayed emesis may occur. Choice of antiemetic regimen depends primarily on the emetogenic potential and the risk of delayed CINV associated with the chemotherapy agents. The period of risk for CINV may be up to three days after administration of highly emetogenic chemotherapy (HEC) and at least two days after moderately emetogenic chemotherapy (MEC).[10]
  - For the prevention of CINV post-HEC, triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[10-11]
  - The updated 2015 National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend one specific regimen over another.[10]
  - For the prevention of CINV post-MEC, a 5-HT_3 receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being optional.[10-12]
  - Guidelines generally recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention CINV associated with MEC. Adjunctive therapies include with lorazepam, an H_2 receptor antagonist or a proton pump inhibitor.[10-12]
  - The Pediatric Oncology Group of Ontario in 2012 recommend aprepitant in combination with granisetron and dexamethasone in children 12 years of age or older who will be receiving HEC and in which the antineoplastics are not known to or suspected of interacting with aprepitant. Dual therapy with ondansetron or granisetron and dexamethasone is recommended if the antineoplastic agents interact with aprepitant.[13]
  - Several guidelines have not yet been updated to include netupitant/palonosetron and/or rolapitant.[11-13]
  - According to the Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy, more severe cases should be treated with pyridoxine monotherapy first-line. If monotherapy is inadequate, guidelines recommend pyridoxine in combination with doxylamine. If combination therapy failed, promethazine or dimenhydrinate can be substituted for doxylamine. Other third-line options include metoclopramide, ondansetron, trimethobenzamide or methylprednisolone.[14]

- Other Key Facts:
  - Doxylamine/pyridoxine is the only FDA-approved agent for the treatment of nausea and vomiting of pregnancy.
  - All NK_1 antagonists are formulated as either an oral capsule or tablet, with the exception of fosaprepitant, which is an intravenous injection. Aprepitant is also formulated as an oral suspension.[1-4]
  - For HEC, fosaprepitant, rolapitant, and netupitant/palonosetron are given only on day one as a single dose, while aprepitant is given for three days.[1-4]
  - Doxylamine/pyridoxine is initially given once daily at bedtime (two tablets) but may be increased to twice daily (one tablet in the morning and two tablets at bedtime). The maximum dose is two tablets in the morning and two tablets at bedtime (four tablets/day).[5]
  - All NK_1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-4]
  - Aprepitant oral suspension and capsules are the only NK_1 antagonist currently approved by the FDA for use in pediatric patients.[1-4]

- Both the FDA-approved label and clinical guidelines do not recommend aprepitant for patients less than 12 years of age, however, the oral suspension has been shown to be safe and effective in patients 6 months of age and older.[1,13]
- Due to its co-formulation, netupitant/palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[4]

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