Aprepitant (Emend®)
Merck & Co., Inc.

In the US, aprepitant, when used with other antiemetic agents, is indicated for the treatment of acute and delayed nausea due to highly emetogenic chemotherapy (including cisplatin).\(^1\)

Aprepitant was approved by the US Food and Drug Administration (FDA) on March 26, 2003 and was launched on April 14, 2003.\(^2\) Aprepitant is now under review by Health Canada and a potential Canadian marketing date has not been established (Dr. Ernest Pregent, Merck Frosst Canada Ltd., Kirkland, Quebec: personal communication, 2003 May 20).

Aprepitant is a substance P or neurokinin 1 (NK\(_1\)) antagonist. Substance P is one of four tachykinins found in neurons that are involved in the induction of vomiting.\(^1\) Substance P mediates its biological effects through the NK\(_1\)-receptor. Aprepitant has little or no affinity for other emetogenic receptors including serotonin (5-HT\(_3\)), dopamine and corticosteroid.\(^1\) Aprepitant has been evaluated for its antiemetic activity when used with ondansetron (a 5-HT\(_3\) receptor antagonist) and dexamethasone (a corticosteroid).\(^1\)

Agents that are used for treating or preventing chemotherapy-induced nausea and vomiting (CINV) include 5-HT\(_3\) antagonists (dolasetron, granisetron, ondansetron), corticosteroids (dexamethasone, methylprednisolone), metoclopramide, neuroleptics (prochlorperazine, droperidol, haloperidol), benzodiazepines (alprazolam, diazepam, lorazepam), cannabinoids (nabilone, dronabinol) and antihistaminics or anticholinergics (diphenhydramine, scopolamine).\(^3,4\) The standard treatment for acute nausea and vomiting associated with highly emetogenic chemotherapy combines a 5-HT\(_3\) antagonist with a corticosteroid. Delayed nausea and vomiting due to highly emetogenic chemotherapy is managed with one of the following combinations: dexamethasone with metoclopramide, a 5-HT\(_3\) antagonist or prochlorperazine; or dexamethasone alone.\(^3,4\)

The cost of aprepitant in the US is US$250 for a standard three-day course of therapy (125 mg on day 1 and 80 mg daily on days 2 and 3).\(^2\) There is no Canadian price for aprepitant at this time.

The American approval of aprepitant was based on two multicentre, randomized, double-blind, parallel group, active controlled trials. The results of these trials have not been published, but detailed information was presented in the new drug application, which was accessed through the FDA's web site.\(^5,6\) Over 1,000 subjects were included in the analysis.
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(n=530 in protocol 052 and n=569 in protocol 054). The studies evaluated the efficacy of aprepitant in combination with dexamethasone and ondansetron for preventing CINV in cisplatin-naive patients who received cisplatin (dosage ≥70 mg/m²). Other chemotherapy was permitted. Emetogenic agents such as doxorubicin and cyclophosphamide had to be administered with cisplatin on day 1 to ensure a consistent emetogenic stimulus. Primary objectives for both studies included complete response (no emesis or rescue medications) for the first 120 hours after the start of cisplatin chemotherapy and safety of the triple therapy. The triple regimen consisted of aprepitant 125 mg PO on day 1 and 80 mg PO daily on days 2 and 3; dexamethasone 12 mg PO on day 1 and 8 mg PO daily on days 2 to 4; and ondansetron 32 mg IV on day 1. The standard therapy included dexamethasone 20 mg PO on day 1, then 8 mg PO bid on days 2 to 4; and ondansetron 32 mg IV on day 1. A complete response for 120 hours was observed in significantly more subjects in the aprepitant group than in the control group (i.e., 72.7% versus 52.3% in protocol 052 and 62.7% versus 43.3% in protocol 054, p<0.001). Aprepitant was also significantly better than control when data were separated for acute and delayed phases. There was a trend towards improved nausea scores with aprepitant, but they did not reach statistical significance in protocol 052 and only a few parameters reached statistical significance in protocol 054.

Data on aprepitant for CINV from two other controlled trials have been published. The dosages of aprepitant used in these trials, however, differ from those approved by the FDA, so details from these studies will not be disclosed in this review. In one study, the dosage of aprepitant was 400 mg PO daily for six days. In the other study, aprepitant's pro-drug (L-758,298) was given as an intravenous injection on day 1 followed by oral aprepitant 300 mg daily for four more days.

Determining the true incidence of adverse effects due to aprepitant is difficult since it was used with ondansetron and dexamethasone in the large clinical trials. Adverse effects that were reported more often with the aprepitant-ondansetron-dexamethasone combination over the ondansetron-dexamethasone combination include abdominal pain, diarrhea, epigastric discomfort, dehydration, dizziness, gastritis, heartburn, anorexia and hiccups. Adverse effects were described as mild to moderate in intensity. Drugs that are metabolized by CYP450 3A4 or 2C9 should be used with caution by patients taking aprepitant. Aprepitant seems to offer a significant advantage for treating vomiting when used with standard therapy (i.e., dexamethasone and a 5-HT₃ antagonist). The larger clinical trials, however, failed to show a statistically significant improvement with aprepitant when only nausea was evaluated. The FDA reviewer raised concern about the definition of highly emetogenic doses of cisplatin being equal to or greater than 70 mg/m². In the ondansetron submission, the highly emetogenic dose of cisplatin was between 100 and 120 mg/m².
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Whether the significant reduction in vomiting observed with aprepitant in these studies would be maintained at higher doses of cisplatin is yet to be proven. More research with higher cisplatin doses would be useful in determining aprepitant's place following highly emetogenic chemotherapy.

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada. These summaries have not been externally peer reviewed.

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