

# Aprepitant Capsules

(Emend® — Merck & Co., Inc.)

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Chemotherapy-induced nausea and vomiting (CINV) are among the most troubling side effects of cancer treatment.<sup>1</sup> Significant improvements in the prevention and treatment of CINV have been made in the past 15 years as the understanding of the mechanisms involved in nausea and vomiting has increased. However, delayed CINV, defined as that occurring more than 24 hours after the administration of chemotherapy, remains a difficult problem with highly emetogenic regimens, such as those including cisplatin.<sup>2</sup> While ample evidence exists supporting the efficacy of many other antiemetics for the prevention and treatment of delayed CINV, aprepitant is the first antiemetic specifically approved by the FDA for this use.

## PHARMACOLOGY

Aprepitant is a substance P antagonist active at the neurokinin 1 (NK<sub>1</sub>) receptor in the central nervous system.<sup>3</sup> Its pharmacologic effects are not related to activity at dopamine, 5-HT<sub>3</sub>, or corticosteroid receptors. Substance P is a neuropeptide released by sensory neurons in response to radiation or emetogenic substances.<sup>4</sup> Its role in inducing emesis is exerted at the NK<sub>1</sub> receptors found in the area postrema and the nucleus tractus solitarius. NK<sub>1</sub>-receptor antagonists inhibit emesis caused by a wide variety of substances, including antineoplastic drugs. Aprepitant inhibits acute and delayed emesis caused by cisplatin and enhances the antiemetic properties of 5-HT<sub>3</sub> antagonists and corticosteroids.<sup>3</sup>

## PHARMACOKINETICS

Aprepitant is absorbed orally with a bioavailability of 60-65%.<sup>3</sup> Absorption is not significantly affected by food. The peak plasma concentration occurs four hours after administration. Protein binding is greater than 95% and the apparent volume of distribution is 70 L. Aprepitant is metabolized in the liver by cytochrome P450 enzymes, mostly by CYP3A4, but CYP1A2 and CYP2C19 play a minor role. Metabolism of aprepitant produces a number of weakly active metabolites. Metabolism, rather than renal excretion, is the primary means of elimination of aprepitant; metabolites are excreted both in urine and feces. Aprepitant has a terminal half-life of 9 to 13 hours, with a clearance of 62 to 90 mL/min.

The AUC of aprepitant is increased by 10 to 18% in patients with moderate hepatic insufficiency. No dosage adjustment is necessary in these patients. No data are available to guide dosing in patients with severe (Child-Pugh score >9) hepatic insufficiency. The Child-Pugh score is a 15-point system for rating the degree of hepatic impairment in terms of five clinical measures: hepatic

## Summary

**Indications.** Aprepitant is indicated, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

**Monitoring parameters.** Patients should be monitored for a reduction in episodes of nausea and vomiting; adverse effects include fatigue, dizziness, diarrhea and hiccups.

**Dose.** The recommended dose of aprepitant is 125 mg by mouth one hour prior to chemotherapy on day 1, and 80 mg by mouth in the morning on days 2 and 3. Aprepitant should be used in combination with a corticosteroid and a 5-HT<sub>3</sub> antagonist.

**Pediatrics.** Aprepitant has not been evaluated in patients younger than 18 years old.

**Geriatrics.** No dosage adjustment required for geriatric patients.

**Race.** No dosage adjustment required based on race.

**Renal insufficiency.** No dosage adjustment required for patients with renal insufficiency or on hemodialysis.

**Hepatic insufficiency.** No dosage adjustment required for patients with mild-moderate hepatic insufficiency; no data available from patients with severe (Child-Pugh score >9) hepatic insufficiency

**Pregnancy category.** B

**Breastfeeding.** Aprepitant is known to be excreted in the milk of rats. No human studies of breast milk excretion have been performed. Because aprepitant may cause serious adverse effects in the nursing infant, and because it is tumorigenic in animals, the risk vs. benefit of aprepitant use in breastfeeding women should be carefully considered.

**Cost.** The AWP for aprepitant in 30-capsule bottles is \$110.00 for each 125 mg capsule and \$101.23 for each 80 mg capsule, for a total cost of \$312.46 for three days of therapy. A 3-day dose pack, consisting of one 125 mg capsule and two 80 mg capsules, is available for the same cost. The AWP for standard therapy consisting of 32 mg ondansetron IV with dexamethasone 20 mg by mouth on day 1 followed by 3 days at 8 mg per day is \$235.89.

TABLE 1

HIGHLY EMETOGENIC CHEMOTHERAPY REGIMENS<sup>2</sup>

Emesis in > 90% of patients if no antiemetic prophylaxis	Emesis in 60-90% of patients if no antiemetic prophylaxis	Delayed emesis potential
Carmustine > 250 mg/m <sup>2</sup>	Carboplatin	Carboplatin ≥ 50 mg/m <sup>2</sup>
Cisplatin ≥ 50 mg/m <sup>2</sup>	Carmustine ≤ 250 mg/m <sup>2</sup>	Cisplatin ≥ 300 mg/m <sup>2</sup>
Cyclophosphamide > 1500 mg/m <sup>2</sup>	Cisplatin < 50 mg/m <sup>2</sup>	Cyclophosphamide ≥ 600-1000 mg/m <sup>2</sup>
Dacarbazine	Cyclophosphamide > 750 mg/m <sup>2</sup>	Doxorubicin ≥ 50 mg/m <sup>2</sup>
Mechlorethamine	Cytarabine > 1g/m <sup>2</sup>	
Streptozocin	Doxorubicin > 60 mg/m <sup>2</sup>	
	Methotrexate > 1000 mg/m <sup>2</sup>	
	Procarbazine (oral)	

encephalopathy, ascites, total bilirubin, serum albumin and coagulation time. A score of 5 indicates no hepatic dysfunction, while higher scores indicate increasing dysfunction. The AUC and maximum serum concentration of unbound and protein-bound aprepitant are reduced in patients with severe renal insufficiency; because protein binding is decreased in these patients, the AUC of active, unbound aprepitant is not greatly changed compared to patients with normal renal function. The pharmacokinetics of aprepitant are not appreciably affected by hemodialysis. It is not necessary to adjust the dose of aprepitant in patients with renal insufficiency or in those who are on hemodialysis.

### CLINICAL TRIALS

In a 159-patient, randomized, placebo-controlled, double-blind trial, aprepitant significantly reduced both acute and delayed vomiting induced by cisplatin.<sup>5</sup> The subjects were patients without prior exposure to cisplatin who were to receive a single dose of cisplatin 70 mg/m<sup>2</sup> or greater. Each patient was treated with dexamethasone 20 mg by mouth and granisetron 10 mcg/kg IV thirty minutes prior to cisplatin administration. The patients were randomized to three groups as shown in Table 2.

The patients maintained diary cards on which they recorded episodes of vomiting or retching during the 5-day study period. Separate episodes of vomiting or retching were defined as episodes occurring at least one minute apart. Patients evaluated their nausea over each 24-hour period with a 100 mm visual analog scale, where 0 mm indicated the absence of nausea and 100 mm was the worst possible nausea. Patients' overall satisfaction with their antiemetic regimen was evaluated on days 2 through 6 with another 100 mm visual analog scale, where 0 indicated no satisfaction and 100 indicated complete satisfaction. Monitoring for adverse events continued until the patients returned to the clinic for follow up, a time ranging from 17 to 29 days after cisplatin administration. The safety of the regimens was evaluated by analysis of blood, serum chemistry and urine and by physical exams twice, between study days 6 to 8 and days 17 to 29. The primary endpoints were acute and delayed emesis. Self-assessed nausea and use of rescue medication were secondary endpoints.

Acute-phase emesis was significantly lower among patients who received one or more doses of aprepitant, with 93% of patients in group 1 and 94% of patients in group 2 reporting no emesis, compared with 67% of patients in group 3 ( $p < 0.001$  for both 1 and

2 compared to 3). Delayed-phase emesis was similarly reduced in both aprepitant groups, with 82% of patients in group 1 and 78% of patients in group 2 reporting no emesis on days 2 to 5 compared with 33% of patients in group 3 ( $p < 0.001$  for both 1 and 2 compared to 3). The difference in delayed-phase emesis between groups 1 and 2 was not significant.

Groups 1 and 2 also reported significant reductions in nausea ratings compared with group 3 with 49% of patients in group 1 and 48% of patients in group 2 compared to 25% of patients in group 3 reporting minimal or no nausea on days 1-5 ( $p = 0.02$  for group 1 vs. group 3 and  $p = 0.03$  for group 2 vs. group 3). Global satisfaction scores did not differ among the three groups on day 2. On day 6, the median analog scores were 100 mm and 98 mm in groups 1 and 2, respectively, and 82 mm in group 3 ( $p = 0.001$  for 1 vs. 3 and  $p = 0.03$  for 2 vs. 3). No significant differences were observed between the groups in the reporting of adverse effects or in laboratory tests evaluating safety.

Campos et al conducted a similar study in which 351 patients without prior exposure to cisplatin were randomized to one of four treatment groups (see Table 3) prior to receiving their first dose of cisplatin 70 mg/m<sup>2</sup> or greater.<sup>6</sup> Day 1 treatments were administered 30 minutes before cisplatin.

Patients recorded episodes of vomiting or retching, self-assessment of nausea and global satisfaction as described in the previous study. Adverse events and safety were assessed in the same manner as the previous study. The greatest prevention of acute emesis was seen in Group 2, the patients receiving all three components of treatment (80% of patients with no acute episodes of emesis vs. 57% in group 1;  $p < 0.01$ ). The number of patients in group 1 with no acute vomiting was larger than the number from groups 3 or 4 with no acute vomiting (57% vs. 46% and 43%, respectively; 90% CI -24% to 2% difference).

Delayed emesis was significantly decreased in all patients who received aprepitant. Twenty-nine percent of patients in group 1 had no episodes of delayed-phase emesis compared with 63% of group 2 patients, 51% of group 3 patients and 57% of group 4 patients ( $p < 0.01$  for group 2, 3 or 4 vs. group 1). None of the study groups received only a single dose of aprepitant, so it was not possible to confirm the efficacy of a single dose that was demonstrated in the Navari study.

The three-drug regimen of group 2 also significantly reduced acute nausea ratings compared to group 1 ( $p < 0.05$ ). Nausea ratings

**TABLE 2. STUDY GROUPS, NAVARI ET AL.**

	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>
Day 1	Dexamethasone 20 mg PO Granisetron 10 mcg/kg IV Aprepitant 400 mg PO	Dexamethasone 20 mg PO Granisetron 10 mcg/kg IV Aprepitant 400 mg PO	Dexamethasone 20 mg PO Granisetron 10 mcg/kg IV Placebo
Day 2	Aprepitant 300 mg PO	Placebo	Placebo
Day 3	Aprepitant 300 mg PO	Placebo	Placebo
Day 4	Aprepitant 300 mg PO	Placebo	Placebo
Day 5	Aprepitant 300 mg PO	Placebo	Placebo

**TABLE 3. STUDY GROUPS, CAMPOS ET AL.**

	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>
Day -1	Placebo	Placebo	Apr 400 mg PO	Placebo
Day 1	Dex 20 mg PO Gra 10 mcg/kg IV Placebo PO	Dex 20 mg PO Gra 10 mcg/kg IV Apr 400 mg PO	Dex 20 mg PO Placebo IV Apr 400 mg PO	Dex 20 mg PO Placebo IV Apr 400 mg PO
Day 2	Placebo	Apr 300 mg PO	Apr 300 mg PO	Apr 300 mg PO
Day 3	Placebo	Apr 300 mg PO	Apr 300 mg PO	Apr 300 mg PO
Day 4	Placebo	Apr 300 mg PO	Apr 300 mg PO	Apr 300 mg PO
Day 5	Placebo	Apr 300 mg PO	Apr 300 mg PO	Apr 300 mg PO

Apr = aprepitant Dex = dexamethasone Gra = granisetron

**TABLE 4. STUDY GROUPS, VAN BELLE ET AL.**

	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>
Day 1	L-758,298 100 mg IV Dexamethasone 20 mg IV	L-758,298 100 mg IV Dexamethasone 20 mg IV	Ondansetron 32 mg IV Dexamethasone 20 mg IV
Day 2	Aprepitant 300 mg PO	Placebo	Placebo
Day 3	Aprepitant 300 mg PO	Placebo	Placebo
Day 4	Aprepitant 300 mg PO	Placebo	Placebo
Day 5	Aprepitant 300 mg PO	Placebo	Placebo

**TABLE 5. STUDY GROUPS, CHAWLA ET AL.**

	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>
Day 1	Dexamethasone 20 mg PO Granisetron 32 mg IV Aprepitant 125 mg PO	Dexamethasone 20 mg PO Granisetron 32 mg IV Aprepitant 80 mg PO	Dexamethasone 20 mg PO Granisetron 32 mg IV Placebo
Day 2	Dexamethasone 8 mg PO Aprepitant 40 mg PO	Dexamethasone 8 mg PO Aprepitant 25 mg PO	Dexamethasone 8 mg PO Placebo
Day 3	Dexamethasone 8 mg PO Aprepitant 40 mg PO	Dexamethasone 8 mg PO Aprepitant 25 mg PO	Dexamethasone 8 mg PO Placebo
Day 4	Dexamethasone 8 mg PO Aprepitant 40 mg PO	Dexamethasone 8 mg PO Aprepitant 25 mg PO	Dexamethasone 8 mg PO Placebo
Day 5	Dexamethasone 8 mg PO Aprepitant 40 mg PO	Dexamethasone 8 mg PO Aprepitant 25 mg PO	Dexamethasone 8 mg PO Placebo

**TABLE 6. STUDY GROUPS, POLI-BIGELLI ET AL.**

	Group 1	Group 2
Day 1	Dexamethasone 12 mg PO Ondansetron 32 mg IV Aprepitant 125 mg PO	Dexamethasone 20 mg PO Ondansetron 32 mg IV Placebo
Day 2	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO BID Placebo
Day 3	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO BID Placebo
Day 4	Dexamethasone 8 mg PO	Dexamethasone 8 mg PO BID

on day 2-5 were significantly lower in group 3 than in group 1 ( $p < 0.05$ ). For day 2 only, groups 2, 3 and 4 had lower nausea ratings than group 1, but statistical significance was reached only in group 4 vs. group 1 ( $p < 0.05$ ). Groups 2, 3 and 4 had higher percentages of patients with little or no nausea on days 1-5 combined and days 2-5 combined, but statistical significance was not reached. On days 1-5, 36% of patients in group 1 had little or no nausea, compared to 50%, 41% and 44% in groups 2, 3 and 4, respectively ( $p < 0.07$  for 2 vs. 1). On days 2-5, 38% of patients in group 1 had little or no nausea vs. 52%, 45% and 49% for groups 2, 3 and 4, respectively ( $p < 0.07$ ). There were no significant differences between the groups in global satisfaction scores, nor were there significant differences in adverse effects.

A third study evaluated aprepitant and its prodrug, L-758,298, in the prevention of acute and delayed emesis in 177 patients receiving cisplatin for the first time, all at doses 70 mg/m<sup>2</sup> or greater.<sup>7</sup> The patients were randomized into one of three groups as shown in Table 4.

L-758,298 and ondansetron doses were administered one hour prior to cisplatin; dexamethasone was administered 30 minutes prior. Vomiting, retching, nausea ratings, global satisfaction ratings, safety and adverse effects were recorded as in the two previous studies.

Significantly more patients in group 3 had no acute emesis and no use of rescue medication than patients in group 1 or 2 or in groups 1 and 2 combined (83% for group 3 vs. 44% and 36% in groups 1 and 2 respectively; 40% for groups 1 and 2 combined;  $p < 0.001$  for group 3 vs. 1 and 2 combined). When the data are analyzed without regard to rescue medication use, Group 3 is again significantly superior to groups 1 and 2 (84% with no acute vomiting in group 1 vs. 49% and 47%, respectively, and 48% for 1 and 2 combined;  $p < 0.001$  for 3 vs. 1 and 2 combined).

Groups 1 and 2 had more patients without delayed-phase emesis or rescue medication use than did group 3 (59% and 46% vs. 38%, respectively). The difference between group 1 and group 3 was statistically significant ( $p < 0.05$ ). When use of rescue medication is not considered, groups 1 and 2 are significantly superior to group 3 (65% and 61%, respectively, with no emesis vs. 41%;  $p < 0.05$  for group 1 or 2 vs. group 3).

Acute nausea ratings were lower in group 3 than in group 1 or 2 (median 1 mm vs. 11 mm for 1 and 2 combined;  $p < 0.05$ ). There were no significant differences between groups in either delayed-

**TABLE 7. HESKETH ET AL.**

	Group 1	Group 2
Day 1	Dexamethasone 12 mg PO Ondansetron 32 mg IV Aprepitant 125 mg PO	Dexamethasone 20 mg PO Ondansetron 32 mg IV Placebo
Day 2	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO BID Placebo
Day 3	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO BID Placebo
Day 4	Dexamethasone 8 mg PO	Dexamethasone 8 mg PO BID

phase nausea or nausea over the entire interval. The percentage of patients with little or no delayed nausea ( $\leq 5$  mm on visual analog scale) was 38%, 46% and 50% in group 1, 2 and 3, respectively. The percentage of patients with little or no nausea in the treatment period overall was 33%, 37% and 46% in group 1, 2 and 3, respectively. Global satisfaction ratings at 24 hours after cisplatin were significantly superior in group 3 compared to groups 1 and 2 combined (99 mm vs. 91 mm, respectively;  $p < 0.005$  for 3 vs. 1 and 2 combined). On the sixth day, global satisfaction ratings were not significantly different among the three groups. More patients in groups 1 and 2 reported diarrhea (23% in each group vs. 5% in group 3); otherwise, adverse effects did not differ significantly.

A randomized, double-blind, placebo-controlled study compared two dose regimens of aprepitant and placebo in combination with ondansetron and dexamethasone in patients receiving their first dose of cisplatin ( $\geq 70$  mg/m<sup>2</sup>).<sup>8</sup> Patients were randomized into one of three groups, as shown in Table 5.

The doses of aprepitant in group 2 were reduced from 375 mg on day 1 and 250 mg on days 2 to 5 after it was discovered that the blood levels of aprepitant in that group were unexpectedly high and that there was a drug interaction between aprepitant and dexamethasone. After the dose adjustment was made, 381 patients were enrolled in the study; 377 of those patients were evaluable for the primary analysis of results.

Episodes of vomiting and retching, self-assessments of nausea, tolerability and safety were measured as in the previous studies. There was a higher percentage of patients in both aprepitant groups who had a complete response to therapy, defined as no vomiting and no use of rescue medication (71% in group 1, 58.8% in group 2 and 43.7% in group 3;  $p < 0.01$  for 1 vs. 2 and  $p < 0.05$  for 2 vs. 3). For acute-phase emesis alone, 83.2% of patients in group 1 had a complete response, compared to 75.6% in group 2 and 71.4% in group 3 ( $p = 0.014$  for 1 vs. 3). For delayed-phase emesis alone, both aprepitant groups had significantly more subjects with a complete response (72.7% for group 1, 63.9% for group 2 and 45.2% for group 3;  $p < 0.001$  for group 1 vs. group 3 and  $p < 0.002$  for group 2 vs. group 3).

The secondary endpoints evaluated were no emesis, no rescue, no nausea, no significant nausea, complete protection (no emesis or rescue therapy and no significant nausea) and total control (no emesis or rescue therapy and no nausea). In the acute phase, group 1 had significantly more patients with no emesis ( $p < 0.01$ ) and

TABLE 8. DEWIT ET AL.

	Group 1	Group 2	Group 3
Day 1	Dexamethasone 12 mg PO Ondansetron 32 mg IV Aprepitant 375 mg PO	Dexamethasone 20 mg PO Ondansetron 32 mg IV Aprepitant 125 mg PPO	Dexamethasone 20 mg PO Ondansetron 32 mg IV Placebo
Day 2	Dexamethasone 8 mg PO Aprepitant 250 mg PO	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO Placebo
Day 3	Dexamethasone 8 mg PO Aprepitant 250 mg PO	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO Placebo
Day 4	Dexamethasone 8 mg PO Aprepitant 250 mg PO	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO Placebo
Day 5	Dexamethasone 8 mg PO Aprepitant 250 mg PO	Dexamethasone 8 mg PO Aprepitant 80 mg PO	Dexamethasone 8 mg PO Placebo

complete protection ( $p < 0.05$ ) than group 3. There were no other significant differences in the acute phase. In the delayed phase, group 1 had significantly better results on all secondary endpoints than group 3 ( $p < 0.01$  for all secondary endpoints). Group 2 had significantly better results for no emesis, no nausea, complete protection and total control ( $p < 0.01$  for all) as well as for no rescue therapy ( $p < 0.05$ ). In the overall evaluation, group 1 had significantly better results than group 3 on all secondary outcomes ( $p < 0.01$  for all), and group 2 had significantly better results than group 3 for no emesis ( $p < 0.01$ ) and for no nausea, complete protection, and total control ( $p < 0.05$ ).

The most commonly reported adverse effects in all groups were asthenia/fatigue, constipation, diarrhea, nausea, neutropenia, anorexia, headache and hiccups. Adverse effects were more common among patients in group 1, although the differences between the groups were not significant (RR=1.06;  $p=0.448$ ). No dose-response relationship was noted for adverse events. There were no significant differences between the groups in adverse events that were considered drug-related (RR=1.05;  $p=0.831$ ) or in the number of patients withdrawing from therapy because of adverse events (RR=1.32;  $p=0.804$ ). The aprepitant groups had more serious clinical adverse events as defined by the study protocol than did group 3 (21.5% in group 1, 16.7% in group 2 and 12.3% in group 3; RR=1.75 for group 1 vs. group 3;  $p=0.032$ ).

Another randomized, double-blind, placebo-controlled study demonstrated the superiority of the 125 mg/ 80 mg/ 80 mg regimen of aprepitant over standard therapy.<sup>9</sup>

The patients in the study were receiving cisplatin for the first time at doses 70 mg/m<sup>2</sup> or greater. Aprepitant or placebo was administered one hour prior to initiating the cisplatin infusion; ondansetron and dexamethasone were administered 30 minutes before cisplatin. In patients who were to receive either paclitaxel or docetaxel in addition to the cisplatin, a 20 mg dose of dexamethasone was given 12 hours and 6 hours prior to administration of the taxane, and no dose of dexamethasone was given 30 minutes prior to the cisplatin (see Table 6).

Episodes of vomiting or retching and self-assessments of nausea were recorded as in the previous studies. Data was also gathered on rescue medication use and a Functional Living Index-Emesis (FLIE) questionnaire was filled out on day 6. The FLIE

questionnaire is a tool for measuring the impact of CINV on patients' quality of life. It consists of 18 questions, each scored on a 7-point scale with 18 being the lowest total score and higher scores indicating increasing quality of life to a maximum score of 126. Safety and tolerability were assessed as in the previous studies. The primary endpoint was complete response, defined as no vomiting and no use of rescue therapy. Secondary endpoints were complete protection, defined as no emesis, no use of rescue medication and no significant nausea; total control, defined as no emesis, no use of rescue medication and no nausea; no nausea; FLIE scores; no significant nausea, defined as <25 mm on the visual analog scale; and no nausea, defined as <5 mm on the visual analog scale. Differences between the two groups in incidence of febrile neutropenia, thought to be possible due to an interaction between aprepitant and dexamethasone, and serious adverse effects to chemotherapy, potentially attributable to CYP3A4 inhibition by aprepitant, were also recorded.

The aprepitant group (group 1) had a significantly greater percentage of patients with complete responses overall than did group 2 (62.7% vs. 43.3%;  $p < 0.001$ ). Group 1 also had significantly more complete responses than group 2 in both the acute (day 1) and delayed (days 2-5) phases when the phases were analyzed separately. For the acute phase, 82.2% of patients in group 1 had complete responses, compared to 68.4% in group 2 ( $p < 0.001$ ). Complete response rates for the delayed phase were 67.7% for group 1 and 46.8% for group 2 ( $p < 0.01$ ). Significantly more patients in group 1 had no emesis, no rescue therapy and complete protection overall and in both the acute and delayed phases compared to group 2. A significantly higher percentage of patients in group 1 had total control and no nausea overall and in the delayed phase. There was not a significant difference in the number of patients having no significant nausea overall and in the delayed phase between the two groups. Rates of no nausea and no significant nausea were not analyzed for the acute phase.

There were no significant differences between the two groups in the numbers of adverse events, drug-related adverse events, laboratory value abnormalities and patients discontinuing treatment because of adverse events. There were 24 deaths during the study period, none of which were considered drug-related. The number of deaths was similar in both groups. The most commonly

**TABLE 9. SUMMARY OF PUBLISHED SINGLE-CYCLE TRIALS; ALL PLACEBO-CONTROLLED**

Ref.	Group (n)	Day -1	Day 1	Days 2-5	Resp <sup>1</sup>	Resp <sup>2</sup>	<i>P acute P delayed</i>
5	1 (54)	—	Dex 20 mg PO Gra 10 mcg/kg IV Apr 400 mg PO	Apr 300 mg PO	77%	52%	0.004 <sup>3</sup> 0.001
5	2 (54)	—	Dex 20 mg PO Gra 10 mcg/kg IV Apr 400 mg PO	Placebo	83%	43%	0.004 <sup>3</sup> 0.001
5	3 (51)	—	Dex 20 mg PO Gra 10 mcg/kg IV	Placebo	57%	16%	0.004 <sup>3</sup> 0.001
6	1 (90)	—	Dex 20 mg PO Gra 10 mcg/kg IV	Placebo	57%	29%	<0.01 <sup>4</sup>
6	2 (86)	—	Dex 20 mg PO Gra 10 mcg/kg IV Apr 400 mg PO	Apr 300 mg PO	80%	63%	<0.01 <sup>5</sup>
6	3 (89)	Apr 400 mg	Dex 20 mg PO Apr 400 mg PO	Apr 300 mg PO	46%	51%	<0.01 <sup>5</sup>
6	4 (86)	—	Dex 20 mg PO Apr 400 mg PO	Apr 300 mg PO	43%	57%	<0.01 <sup>5</sup>
7	1 (61)	—	L 100 mg IV Dex 20 mg IV	Apr 300 mg PO	44%	65%	<0.001 <sup>6</sup> <0.05 <sup>7</sup>
7	2 (58)	—	L 100 mg IV Dex 20 mg IV	Placebo	36%	61%	<0.001 <sup>6</sup> <0.05 <sup>7</sup>
7	3 (58)	—	Ond 32 mg IV Dex 20 mg IV	Placebo	83%	41%	<0.001 <sup>6</sup> <0.05 <sup>7</sup>
8	1 (134)	—	Dex 20 mg PO Ond 32 mg IV Apr 125 mg PO	Dex 8 mg PO Apr 80 mg PO	83.2%	72.7%	0.014 <sup>8</sup> <0.001 <sup>8</sup>
8	2 (120)	—	Dex 20 mg PO Ond 32 mg IV Apr 40 mg PO	Dex 8 mg PO Apr 25 mg PO	75.6%	63.9%	NA 0.002 <sup>9</sup>
8	3 (127)	—	Dex 20 mg PO Ond 32 mg IV	Dex 8 mg PO Placebo	71.4%	45.2%	0.014 <sup>8</sup> 0.001 <sup>8</sup>
9	1 (285)	—	Dex 20 mg PO Ond 32 mg IV	Dex 16 mg PO <sup>10</sup> Placebo	65%	44%	<0.01 <0.01
9	2 (260)	—	Dex 20 mg PO Ond 32 mg IV Apr 125 mg PO	Dex 16 mg PO <sup>10</sup> Apr 80 mg PO <sup>11</sup>	80%	61%	<0.01 <0.01
10	1 (264)	—	Dex 20 mg PO Ond 32 mg IV Apr 125 mg PO	Dex 8 mg PO <sup>12</sup> Apr 80 mg PO <sup>11</sup>	89.2%	75.4%	<0.001 <0.001
10	2 (266)	—	Dex 20 mg PO Ond 32 mg IV	Dex 16 mg PO <sup>10</sup> Apr 80 mg PO <sup>11</sup>	78.1%	55.8%	<0.001 <0.001

Dex – dexamethasone; Gra – granisetron; Apr – aprepitant; L – L758,298; Ond — ondansetron

<sup>1</sup>Complete response (no emesis, no rescue medication) acute phase (day 1)

<sup>2</sup>Complete response (no emesis, no rescue medication) delayed phase (days 2-5)

<sup>3</sup>Groups 1 and 2 collectively vs. group 3

<sup>4</sup>Group 1 vs. group 2

<sup>5</sup>Groups 2, 3 and 4 collectively vs. group 1

<sup>6</sup>Group 3 vs. groups 1 and 2 collectively

<sup>7</sup>Group 1 or 2 vs. group 3

<sup>8</sup>Group 1 vs. group 3

<sup>9</sup>Group 2 vs. group 3

<sup>10</sup>In 2 doses, on days 2-4 only

<sup>11</sup>Days 2-3 only

<sup>12</sup>Days 2-4 only

reported adverse events were anorexia, asthenia/fatigue, constipation, diarrhea, headache, nausea and vomiting, all of which occurred in at least 10% of patients in one or both groups. There were no significant differences between the two groups in the number of cases of febrile neutropenia or serious infection-related adverse events. The number of chemotherapy-related serious adverse events was higher in group 1 than in group 2 among patients who received chemotherapy that is metabolized by CYP3A4, such as etoposide, taxanes and vinca alkaloids (15.9% vs. 8.5%; statistical significance not indicated). Among patients receiving chemotherapy that is not metabolized by CYP3A4, serious chemotherapy-related adverse reactions were less frequent in group 1 than in group 2 (4.2% vs. 11.6%, statistical significance not indicated).

These results were confirmed in a larger study conducted by Hesketh et al in which 530 patients were randomized to the same treatment regimens as described in the previous study<sup>10</sup> (see Table 7). The patients were receiving their first courses of cisplatin at doses 70 mg/m<sup>2</sup> or greater. The primary endpoint was again complete response (no vomiting and no rescue medication) for the overall study period. Secondary endpoints were the same as in previous studies.

Patients receiving aprepitant had a significantly greater number of complete responses for the overall study period compared to the patients on standard therapy (72.7% vs. 52.3%,  $p < 0.001$ ). The aprepitant group also had significantly more patients with no vomiting, no rescue medication and complete protection. More patients in the aprepitant group had total control, no nausea and no significant nausea, but the difference was not statistically significant.

Patients in the aprepitant group had a significantly longer time to first emesis ( $p < 0.001$ ) and were more likely than recipients of standard therapy to be free of delayed emesis regardless of whether they had vomiting in the acute phase of the study. The rate of adverse effects was similar for both groups and the most common adverse effects in both groups were asthenia or fatigue, constipation, hiccups and nausea.

Aprepitant was compared to standard therapy in prevention of nausea and vomiting over repeated cycles of highly emetogenic chemotherapy<sup>11</sup> (see Table 8). Two dosing regimens of aprepitant were used in the beginning of the study, but when the pharmacokinetics of aprepitant were better understood, the higher-dose arm of the study was discontinued and the patients in that arm were not included in the final analysis of the data.

Patients were eligible for the study if they were adults over 18 years old and were receiving their first course of cisplatin chemotherapy at a dose 70 mg/m<sup>2</sup> or greater. Patients could remain in the study for as many as six cycles of chemotherapy. The efficacy of the treatments was categorized as complete response (no vomiting and no use of rescue medication), partial response (0-2 episodes of vomiting and no use of rescue medication) or failed response ( $> 2$  episodes of vomiting and/or use of rescue medication).

The probability of a complete response to aprepitant plus standard therapy was significantly higher than the probability of a complete response to standard therapy alone in cycles 1, 5 and 6 ( $p < 0.05$ ). In addition, the difference in efficacy between aprepitant/standard therapy and standard therapy alone increased over the course of multiple cycles of chemotherapy. Adverse effects were similar for both groups except for the inci-

dence of febrile neutropenia, which was higher among patients in the aprepitant group. This effect was thought to be caused by a drug interaction between aprepitant and dexamethasone resulting in higher blood levels of dexamethasone, increasing steroid exposure in that group. There was a similar number of withdrawals from the trial in both groups, and the reasons for withdrawal were similar.

## DRUG INTERACTIONS

Aprepitant is metabolized by CYP3A4, and both induces and moderately inhibits the enzyme. It also induces CYP2C9. These enzyme effects may result in interactions with concurrently administered drugs.

- Use of aprepitant is contraindicated in patients taking pimozone, terfenadine, astemizole, or cisapride. Aprepitant should be used with caution in patients receiving other medications that are metabolized by CYP3A4. This includes the following chemotherapy agents:

<i>Docetaxel</i>	<i>Paclitaxel</i>	<i>Etoposide</i>
<i>Irinotecan</i>	<i>Ifosfamide</i>	<i>Imatinib</i>
<i>Vinorelbine</i>	<i>Vinblastine</i>	<i>Vincristine</i>

- Aprepitant may induce the metabolism of the following drugs, reducing their serum levels and possibly causing a treatment failure with these drugs:

<i>Warfarin</i>	<i>Phenytoin</i>	<i>Tolbutamide</i>
<i>Norethindrone</i>		

- Concurrent administration of aprepitant increases the AUC of the following drugs:

<i>Dexamethasone</i>	<i>Methylprednisolone</i>	<i>Midazolam</i>
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Oral doses of dexamethasone and methylprednisolone should be reduced by 50% and IV doses of methylprednisolone should be reduced by 25% when used concurrently with aprepitant.

- Strong inhibitors of CYP3A4 may cause increased blood levels of aprepitant when administered concurrently. Caution should be exercised when using aprepitant with any of the following drugs, or with other CYP3A4 inhibitors:

<i>Ketoconazole</i>	<i>Itraconazole</i>	<i>Nefazodone</i>
<i>Troleandomycin</i>	<i>Clarithromycin</i>	<i>Ritonavir</i>
<i>Nelfinavir</i>		

- Drugs that are strong inducers of CYP3A4 may lower blood levels and thus decrease the efficacy of aprepitant. Drugs that may cause this interaction include:

<i>Rifampin</i>	<i>Carbamazepine</i>	<i>Phenytoin</i>
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## ADVERSE EFFECTS

In clinical trials, aprepitant was well-tolerated, with only mild-to-moderate adverse effects reported.<sup>3</sup> Most adverse reactions were reported at the same rate as those associated with standard therapy, including abdominal pain, constipation, gastritis, nausea, vomiting, anorexia and headache. Adverse effects reported at a somewhat greater frequency with aprepitant compared to standard therapy included asthenia or fatigue, dizziness, diarrhea, heartburn

and hiccups. In one trial, a group treated with aprepitant 125/80 mg had a higher incidence of infection (13%) than the group receiving standard therapy (4.2%).<sup>8</sup> In that study, the relative risk of a serious adverse event in the group treated with aprepitant compared to the standard therapy group was 1.75 ( $p=0.032$ ).

### COST, DOSE AND HOW SUPPLIED

Aprepitant is available as 125 mg and 80 mg capsules, in bottles of 30 and in unit-dose packages. It is also available in a 3-day dose pack consisting of one 125 mg capsule and two 80 mg capsules. The AWP for aprepitant in 30-capsule bottles is \$110.00 for each 125 mg capsule and \$101.23 for each 80 mg capsule, for a total cost of \$312.46 for three days of therapy. A 3-day dose pack, consisting of one 125 mg capsule and two 80 mg capsules, is available for the same cost. The AWP for standard therapy consisting of 32 mg ondansetron IV with dexamethasone 20 mg by mouth on day 1 followed by 3 days at 8 mg per day is \$235.89.

### CONCLUSION

Aprepitant is effective in reducing delayed nausea and vomiting associated with highly emetogenic chemotherapy, but should be restricted to use in adult patients until information on pediatric use is available. Aprepitant also augments the effects of 5-HT<sub>3</sub> antagonists in reducing acute-phase vomiting, and is most effective when used in combination with a corticosteroid and a 5-HT<sub>3</sub> antagonist. However, given the high cost of this product, combination therapy with 5-HT<sub>3</sub> antagonists should be restricted to patients who have failed on 5-HT<sub>3</sub> antagonist mono-therapy. Combination therapy should not be used in chemotherapy-naïve patients, even when highly emetogenic chemotherapy is administered. Patients who experience refractory delayed nausea and vomiting may consume large doses of 5-HT<sub>3</sub> antagonists. In those cases, the addition of aprepitant can reduce 5-HT<sub>3</sub> antagonist requirements, making combination therapy less expensive than mono-therapy. ●

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## 2004 PSW Legislative Day

March 3

Monona Terrace

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Legislative Day the only program offered by PSW that is dedicated solely to government affairs issues as they relate to pharmacy. This program offers participants an insider's view of the decision making process at the State Capitol and an opportunity to meet with legislators. PSW is known in the Capitol for its informed members and strong grassroots network.

This year's program will include briefings on the changes to the Federal Medicare program and the importation of drugs from Canada. Participants will also have the opportunity to listen to and talk with legislative leaders as they prepare for the final days of the legislative session and look ahead to the fall elections.

Please make arrangements to attend the 2004 Legislative Day in Madison.