National PBM Drug Monograph
Aprepitant (Emend®)
August 2003
VA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction

The purpose of this monograph is to review the clinical data associated with the neurokinin 1 receptor antagonist aprepitant (MK-0869, L-754,030) for chemotherapy-induced nausea and vomiting. Outcomes of interest include the episodes of vomiting in the acute (first 24 hours) and delayed phases (days 2-5) and the episodes of nausea in both the acute and delayed phases. Comparison of aprepitant regimens to current standard regimens is important, as current regimens have no indication for delayed nausea and vomiting.

Pharmacology/Pharmacokinetics[1,2,3,4,5,6,7]

Substance P is a mammalian peptide of the tachykinin family that acts as a neurotransmitter. Substance P is found in the gut and the central nervous system, specifically the vagal afferent fibers that innervate the nucleus tractus solitarii and the area postrema. Substance P binds to a specific neurokinin 1 receptor (NK_1). In animal studies, Substance P applied directly to the nucleus tractus solitarii produced emesis.

Several nonpeptide NK_1 antagonists have been developed and have demonstrated antiemetic activity across a wide variety of emetic stimuli in animal models. Animal models confirm evidence that the antiemetic activity of NK_1 antagonists is dependent on their ability to cross the blood-brain barrier, as a quaternized antagonist prevented cisplatin-induced emesis in ferrets when administered directly into the CNS but not when it was administered peripherally.

	Aprepitant
Metabolism	Metabolized primarily via CYP3A4 with minor metabolism by CYP1A2 and CYP2C9. Seven metabolites identified, but only weakly active.
Elimination	Primarily hepatic metabolism; eliminated primarily by excretion of metabolites (45% in feces and 57% in urine) when IV pro-drug formulation was used. Excretion following oral administration has not been studied.
Half-life	Terminal half-life 9-13 hours
Protein Binding	Greater than 95% bound to plasma proteins in humans
Bioavailability	Mean absolute bioavailability 60-65%, not clinically affected by administration with standard breakfast. Non-linear kinetics producing an increase in AUC 25% greater than dose proportion between 80mg and 125mg doses.

Special Populations
Elderly: Elderly subjects >65 years old show small increases of 36% in AUC. This is not considered clinically significant.

Gender: Women have a slightly lower AUC and a higher Cmax, and a lower half-life when compared to males. None are clinically significant.

Race: The AUC and Cmax were slightly higher in Hispanic subjects when compared to white and black patients. The difference is not clinically significant.

Renal Insufficiency: AUC is 20-40% lower in severe renal impairment and ESRD. Unbound drug concentrations are similar in patients with renal impairment and healthy subjects with normal renal function. Hemodialysis conducted 4 and 48 hours after dose did not affect the pharmacokinetics; less than 0.2% recovered in dialysate.

Hepatic Insufficiency: AUC is up to 20% higher with moderate hepatic impairment. Pharmacokinetics in patients with severe impairment have not been studied.

FDA Approved Indication(s) and Off-label Uses

Aprepitant , in combination with other antiemetics, is indicated for the prevention of acute and delayed nausea and vomiting occurring with initial and repeat courses of highly emetogenic cancer chemotherapy, including cisplatin.

Dosage and Administration[8,9]

Aprepitant is given over 3 days as part of a combination antiemetic regimen that also includes a $5HT_3$ antagonist and a corticosteroid. The recommended dose is 125mg orally 1 hour before chemotherapy on Day 1 and 80mg orally each morning on Days 2 and 3. The starting dose was chosen based on PET scans in normal volunteers showing both a 300mg and a 125mg dose blocked >90% of the NK_1 receptors in the CNS, and the discovery of a pharmacokinetic interaction between aprepitant 375mg and dexamethasone that resulted in increased toxicity. An example of a combination regimen used in clinical trials is given below:

Drug	Day1	Day 2	Day 3	Day 4
Aprepitant	125mg	80mg	80mg	
Dexamethasone	12mg orally	8mg orally in am	8mg orally in am	8mg orally in am
Ondansetron	32mg IV			

Adverse Effects (Safety Data)

Percent Adverse Events in ≥3% of Patients in Phase III Trials

	Aprepitant Regimen (N = 544)	Standard Regimen (N = 550)
Body as a Whole/Unspecified		
Abdominal Pain	4.6	3.3
Asthenia/fatigue	17.8	11.8
Dehydration	5.9	5.1
Dizziness	6.6	4.4
Fever	2.9	3.5
Mucous Membrane Disorder	2.6	3.1
Digestive System		
Constipation	10.3	12.2
Diarrhea	10.3	7.5
Epigastric Discomfort	4	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
EENT		
Tinnitus	3.7	3.8
Heme and Lymph		
Neutropenia	3.1	2.9
Metabolism/Nutrition		
Anorexia	10.1	9.5
Nervous System		
Headache	8.5	8.7
Insomnia	2.9	3.1
Respiratory System		
Hiccups	10.8	5.6

Overall, the incidence of adverse events was similar between the groups.
Serious adverse events occurred in 13.4% of patients in the aprepitant group and 13.5% of patients in the standard therapy group. During Cycle 1, the incidence of infection-related serious adverse events was higher in the aprepitant group: 3.7% versus 2.4% in the standard therapy group.

Pregnancy Category: B- No evidence of teratogenic effects in animal models. No adequate and well-controlled trials in pregnant women.

Nursing Mothers: Unknown if aprepitant is excreted in human milk. It is excreted in the milk of rats. Because of the potential for tumorigenicity in rats, a decision to discontinue nursing or discontinue the drug should be discussed with the mother.

Precautions/Contraindications

Contraindications:
Contraindicated in patients hypersensitive to any component of the product.

Aprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride due to the inhibition of CYP3A4 by aprepitant that potentially could cause serious or life-threatening reactions.

Precautions:
Aprepitant should be used with caution in patients receiving other drugs metabolized via CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs. The effect on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of aprepitant on IV administered CYP3A4 substrates.

Chemotherapy drugs metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Aprepitant was commonly given with etoposide, vinorelbine, and paclitaxel in clinical trials without a dose adjustment for the potential interaction. There were only small numbers of patients receiving docetaxel, vinblastine, vincristine, or ifosfamide and patients should be closely monitored when they are given concomitantly with aprepitant.

Chronic continuous use of aprepitant has not been studied, is not recommended, and could potentially change the drug interaction profile.

Concomitant administration with warfarin may cause an increase in the INR. Patients should be monitored in the 2-week period following the 3-day regimen (especially days 7-10).

The efficacy of oral contraceptives may be reduced, although the effect of the 3-day aprepitant regimen given concomitantly with oral contraceptives has not been studied.

There are no pharmacokinetic studies in patients with severe hepatic insufficiency (Child-Pugh score >9), and caution should be exercised if aprepitant is administered to these patients.

Drug Interactions[10,11,12]

Aprepitant is a substrate for and a moderate inhibitor of CYP3A4. When administered for at least 28 consecutive days, it also becomes an inducer of CYP3A4. In addition, it has also been shown to be an inducer of CYP2C9. Due to first-pass metabolism, the CYP3A4 inhibitory effects of aprepitant are more pronounced when CYP3A4 substrates are given orally.

Corticosteroids: Dexamethasone and methylprednisolone are both metabolized by CYP3A4. In phase IIB trials, aprepitant increased the AUC of IV methylprednisolone 1.3-fold, and increased the AUC of oral dexamethasone 2.3-fold. Subsequent to these findings, the dose of dexamethasone used along with aprepitant was decreased in phase III trials.

$5HT_3$ Antagonists: Ondansetron and granisetron are both primarily metabolized by CYP3A4. Dolasetron is first metabolized by carbonyl reductase to hydrodolasetron, then hydroxylated via CYP2D6 or undergoes N-oxidation via CYP3A4 or flavin monooxygenase. It is the only drug in the class to have warnings about QTc interval prolongation and cardiac effects. Aprepitant has only been studied with IV ondansetron and oral granisetron. Aprepitant did not cause clinically significant effects in these studies. Because the inhibitory effect of aprepitant is greatest with oral substrates of CYP3A4 due of first-pass metabolism, pharmacokinetic data from IV ondansetron cannot be extrapolated to oral ondansetron. There is no pharmacokinetic data on oral ondansetron or IV granistron; there is no data with IV or oral dolasetron or with palonosetron.

Chemotherapy agents: There is no pharmacokinetic data on drug interactions with aprepitant and chemotherapy agents. The most common agents used in the registration trial included cyclophosphamide, etoposide, fluorouracil, gemcitabine, taxanes (paclitaxel and docetaxel), and vinorelbine. Safety data from the registration trial is available with regard to the concomitant use of these agents.
Agents that are CYP3A4 substrates include etoposide, vinca alkaloids (vincristine, vinblastine, and vinorelbine), irinotecan, and ifosfamide.
Cyclophosphamide autoinduces its own metabolism and CYP3A4 does not play a major role in its metabolism.
Doxorubicin is a p-glycoprotein substrate as evidenced by interactions with other p-glycoprotein substrates.
Fluorouracil is eliminated by dihydropyrimidine dehydrogenase.
Gemcitabine is metabolized primarily by cytidine deaminase.

In order to evaluate adverse events potentially related to drug-drug interactions, the sponsor performed additional safety analyses for the most commonly used concomitant chemotherapy agents as well as those chemotherapy agents metabolized by CY3A4.

In patients who received concomitant chemotherapy agents metabolized by CYP3A4, during Cycle 1, there were more infections (3 patients with septic shock, one with sepsis, one with URI), and a higher incidence of neutropenia and febrile neutropenia in the group who received aprepitant.

Safety results for the most common concomitant chemotherapy drugs:
Etoposide (CYP3A4 substrate): Three times as many serious hematologic adverse events occurred in the aprepitant group (8.5% in aprepitant group 3.3% in standard group). Infection was reported in twice as many patients in the aprepitant group (17.9% aprepitant versus 8.8% in standard group).
Fluorouracil: The incidence of serious adverse events was smaller in the aprepitant group, including the incidence of serious hematologic events.
Gemcitabine: The overall incidence of serious adverse events was similar between groups. Febrile neutropenia and thrombocytopenia occurred in 1 patient in the aprepitant group and none in the standard therapy group.
Vinorelbine (CYP3A4 substrate): The overall incidence of serious adverse events was higher in the aprepitant group (15.9% versus 10.5%). The incidence of serious hematologic events was similar. Infection was reported in 18.3% of aprepitant patients and 11.8% of the standard group patients. Serious respiratory events were reported in 7.3% of the aprepitant group and 1.3% of the standard therapy group and included respiratory insufficiency (probably disease progression from lung cancer) and four fatalities.
Paclitaxel (CYP3A4 substrate): The incidence of serious hematologic adverse events was similar in each group. The overall incidence of serious adverse events was similar between groups.
Cyclophosphamide: The incidence of serious and non-serious adverse hematologic events was higher in the aprepitant group (8%) versus the standard group (2.3%). Serious hematologic events occurred in 4% of the aprepitant group versus 0% in the standard group. Infections were reported in 8% of the aprepitant group and 18.6% of the standard group but none were serious.
Doxorubicin: Overall, the incidence of serious adverse events was less in the aprepitant group (2.6%) versus the standard group (7%).
Docetaxel: The overall number of serious adverse events, including hematologic events, was similar between the groups, although the number of patients receiving docetaxel was small.
S-warfarin (CYP2C9 substrate): When administered as part of a three day regimen, aprepitant caused a 34% decrease in S-warfarin trough concentration and a 14% decrease in the INR 5 days after completing the aprepitant dosing.
Oral contraceptives: When given daily for 14 days, aprepitant caused a decrease in the AUC of ethinyl estradiol by 43% and norethindrone by 8%. The 3-day regimen with aprepitant with oral contraceptives has not been studied. Alternative or back-up methods of contraception should be used.
Midazolam(CYP3A4 substrate): Aprepitant increased the AUC of orally administered midazolam by 2.3 fold on day 1 and 3.3 fold on day 5 when midazolam was given concomitantly on days 1 and 5. Although the effects of aprepitant on IV midazolam caused an initial increase in AUC with a subsequent decrease in AUC by day 8, these changes were not considered clinically significant. The co-administration of aprepitant with other benzodiazepines metabolized by CYP3A4 (alprazolam, triazolam) has not been studied, but the potential effects of increased AUC should be considered.
Digoxin: Aprepitant given daily for 5 days along with digoxin in healthy subjects did not affect the pharmacokinetics of digoxin in a short-term pharmacokinetic study.

Effects of agents on aprepitant:
Ketoconazole: A single dose study demonstrated that the AUC of aprepitant increased 5-fold and the terminal half-life increased 3-fold when given concomitantly with 400mg/day of ketoconazole (a strong CYP3A4 inhibitor).

Rifampin: Rifampin (a strong CYP3A4 inducer) 600mg/day plus a single 375mg dose of aprepitant caused a 11-fold decrease in the AUC of aprepitant and a 3-fold decrease in the aprepitant terminal half-life.
Diltiazem: Daily administration of aprepitant 230mg for 5 days with diltiazem resulted in a 2-fold increase in aprepitant AUC and a 1.7-fold decrease in the diltiazem AUC. These effects did not cause clinically meaningful changes in EKG, heart rate, or blood pressure.
Paroxetine: Daily doses of aprepitant with paroxetine caused a decrease in AUC by 25% and C_{max} by 20% for both drugs.

Efficacy Measures

Primary Endpoint:
Overall Complete Response- No emesis and no rescue therapy (0 to 120 hours)

Secondary Endpoints:
Acute Phase Complete Response - 0 to 24 hours
Delayed Phase Complete Response - 25-120 hours
No Emesis – Overall, Acute Phase, and Delayed Phase; includes those using rescue therapy
No Nausea – Overall and Delayed Phase; max nausea VAS <5 mm
No Significant Nausea – Overall and Delayed Phase; max nausea VAS <25 mm
Complete Protection – No emesis, no rescue therapy, no significant nausea (<25 mm on VAS)
Overall, Acute Phase, and Delayed Phase
Total Control – No emesis, no rescue therapy, no nausea (<5 mm on VAS)
Time to First Emesis – 0 to 120 hours

The endpoints and definitions are consistent with current medical literature recommendations for antiemetic trials. The acute phase of nausea and vomiting following cisplatin therapy generally peaks at 6-8 hours after initiation of cisplatin and diminishes at 12 hours. The second phase begins approximately 16-24 hours after initiation of cisplatin and peaks between 25-72 hours, but frequently continues for several days. Serotonin antagonists have been effective during the acute phase but generally are less effective at preventing and treating delayed phase nausea and vomiting.

Risk factors associated with the development of chemotherapy-induced nausea and vomiting include:

Risk Factor	Change in risk
Gender	Females > males
Age	Decreased incidence <6 and >50 years old
Alcohol Consumption	Lower incidence if consuming >10 alcohol units/week
Motion Sickness	Greater risk with prior history
Pregnancy-induced emesis	Greater risk with prior history
Anxiety	Greater risk with high anxiety
Previous chemotherapy cycles	Poor control of nausea and vomiting in previous cycles increases risk in subsequent cycles, including anticipatory symptoms

Clinical Trials[7,13]

Two randomized, double-blind, placebo controlled pivotal studies (052 in the US and 054 International) were completed, and the results were integrated and summarized in the NDA application. (Information on the exact number of patients in each group comes from the FDA medical review and the numbers change depending on the number enrolled, the modified intention-to-treat population, and the number evaluable for adverse events. The number of patients in the modified ITT for aprepitant was 524 and in the standard therapy group was 526).

<table>
<tr><th>Inclusion/Exclusion</th><th>Dose</th><th>Patient Characteristics</th><th>Results</th></tr>
<tr>
<td>1. Cisplatin ≥70mg/m^2 for Cycle 1
2. Solid tumor

Exclusion:
1. Active infection
2. Multi-day course of chemotherapy
3. Radiation to the pelvis or abdomen 1 wk prior or D1-6 of cycle 1
4. Concomitant known substrates, inhibitors, or inducers of CYP3A4
5. Concomitant amifostine

A multiple-cycle extension was available for cycles 2 to a maximum of six)</td>
<td><u>Aprepitant:</u>
Aprepitant 125mg D1
Dex 12 mg po D1
Ond 32mg IV D1

Aprepitant 80mg D2-3
Dex 8mg qam D2-4
PCB qpm D2-4

<u>Standard:</u>
Aprepitant PCB D1
Dex 20mg po D1
Ond 32mg IV D1

Aprep PCB D2-3
Dex 8mg qam D2-4
Dex 8mg qpm D2-4</td>
<td>Stratified according to gender then use of concomitant emetogenic chemotherapy ≥Hesketh level 3

Cycle 1: baseline characteristics of gender, race, age, alcohol consumption, and use of concomitant chemotherapy were similar between the groups

The mean dose of cisplatin was similar between groups

89% of aprepitant patients and 88% of standard group patients were chemo naïve</td>
<td>
<table>
<tr><th></th><th>Aprep %</th><th>Standard %</th></tr>
<tr><td colspan="3">Complete Response (no V , no rescue)</td></tr>
<tr><td colspan="3">Study 052</td></tr>
<tr><td>Overall phase</td><td>72.7**</td><td>52.3</td></tr>
<tr><td>Acute phase</td><td>89.2**</td><td>78.1</td></tr>
<tr><td>Delayed phase</td><td>75.4**</td><td>55.8</td></tr>
<tr><td colspan="3">Study 054</td></tr>
<tr><td>Overall phase</td><td>62.7**</td><td>43.3</td></tr>
<tr><td>Acute phase</td><td>82.8**</td><td>68.4</td></tr>
<tr><td>Delayed phase</td><td>67.7**</td><td>46.8</td></tr>
<tr><td colspan="3">No Nausea (max <5 mm on VAS)</td></tr>
<tr><td colspan="3">Study 052</td></tr>
<tr><td>Overall phase</td><td>47.5</td><td>44.2</td></tr>
<tr><td>Acute phase</td><td>72.3</td><td>69.1</td></tr>
<tr><td>Delayed phase</td><td>51.0</td><td>47.7</td></tr>
<tr><td colspan="3">Study 054</td></tr>
<tr><td>Overall phase</td><td>48.8*</td><td>38.8</td></tr>
<tr><td>Acute phase</td><td>67.7</td><td>66.2</td></tr>
<tr><td>Delayed phase</td><td>52.7**</td><td>39.9</td></tr>
<tr><td colspan="3">No significant nausea (max <25 mm on VAS)</td></tr>
<tr><td colspan="3">Study 052</td></tr>
<tr><td>Overall phase</td><td>73.2</td><td>66.0</td></tr>
<tr><td>Acute phase</td><td>91.0</td><td>86.5</td></tr>
<tr><td>Delayed phase</td><td>75.3</td><td>68.5</td></tr>
<tr><td colspan="3">Study 054</td></tr>
<tr><td>Overall phase</td><td>71.1</td><td>63.9</td></tr>
<tr><td>Acute phase</td><td>90.4*</td><td>82.3</td></tr>
<tr><td>Delayed phase</td><td>72.7</td><td>65.4</td></tr>
<tr><td colspan="3">Complete protection (no V, no rescue, no significant nausea (VAS<25 mm)
Aprepitant group statistically significantly better than standard group in all phases</td></tr>
<tr><td colspan="3">Time to First Emesis
Kaplan-Meier curves show time to first emesis was longer in the aprepitant group starting 16 hours after cisplatin administration</td></tr>
<tr><td colspan="3">Multiple-cycle extension
Time to First Emesis curves show aprepitant group maintained superiority over standard therapy group</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
**p<0.01 *p<0.05
</td>
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Aprepitant, when added to a modified standard antiemetic regimen, was statistically superior to the standard regimen with regard to the primary endpoint of compete response in the overall phase, as well as the secondary endpoints of complete response in the acute and delayed phases. The secondary endpoints of no nausea and no significant nausea reached statistical significance in one study in some of the phases, and the results were not replicated in a second study. The lack of statistical difference in nausea scores is clouded by the higher use of anti-emetic rescue therapy in the standard group. The incidence of most adverse events during cycle 1 was similar between the 2 groups. Events that occurred more frequently (>2% difference) in the aprepitant group included asthenia/fatigue, dizziness, diarrhea, cough, and hiccups. Serious

adverse events that occurred more frequently in the aprepitant group included: infection (3.7% vs 2.4%), dehydration (1.8% vs 0.9% but not seen in the multi-cycle analysis), neutropenia (2.2% vs 1.1%), and respiratory insufficiency (0.9% vs 0.2%). In the multi-cycle analysis, the most frequently sited serious events in the aprepitant group included: dehydration (1.3% vs 1.4%), pneumonia (2% vs 0.9%), neutropenia (2% vs 1.2%), and thrombocytopenia (1% vs 0%).

Laboratory adverse events reported more frequently in the aprepitant group included alkaline phosphatase increase (2.1% vs 0.2%) and aspartate aminotransferase increase (3% vs 1.3%), the majority of which were mild or moderate.

Death due to adverse events was balanced between groups. The incidence of fatal hematologic adverse events was higher in the aprepitant group (0.7% vs 0.2%). The adverse event of respiratory insufficiency resulting in death was more common in the aprepitant group (0.9% vs 0.2%). Four of the five aprepitant patients also received vinorelbine, which can cause pulmonary toxicity and whose kinetics may have been altered by aprepitant. This trend did not continue in the multi-cycle analysis.

Supporting Trials: (see attachment) [2,14,15,16,17]

Several early clinical trials compared aprepitant in a variety of combinations: with dexamethasone on day 1 then alone for 4 more days, added to day 1 of a standard regimen of a $5HT_3$ antagonist plus dexamethasone, added to a standard regimen on day 1 and continued alone for 4 more days. All used doses of 300-400mg, before pharmacokinetic data with dexamethasone revealed increased levels of dexamethasone and increased incidence of infections and before PET scans showed >90% occupancy of CNS NK_1 receptors with lower doses. In the most recent study, the dose of aprepitant was lowered to 125mg/80mg as in the registration trials, but the dexamethasone dose was only changed on days 2-5. In general, these early studies support the registration trial outcomes: aprepitant, when added to a standard antiemetic regimen, decreased the incidence of vomiting in the acute and delayed phases, and sometimes decreased the severity of nausea in the delayed, but not the acute, phase during cycle 1 of chemotherapy that included cisplatin at doses $\geq$70mg/m^2.

Outstanding Issues:
1. Approximately 20% of patients received less than 70mg/m^2 of cisplatin and were included in the efficacy analysis. All patients received >50mg/m^2 of cisplatin. The number of patients receiving the lesser dose was balanced between the groups.
2. Ondansetron was given by IV infusion. The oral dosage form of ondansetron was not studied and a potential drug interaction resulting in higher ondansetron concentrations is expected. The ondansetron dose used is per the package insert but is not commonly used in daily practice.
3. The comparison regimen for prevention of delayed nausea and vomiting was single-agent dexamethasone. While this can be effective, standard practice is to combine dexamethasone with another agent (metoclopramide, prochlorperazine, or rarely a $5HT_3$ antagonist) for best results in preventing delayed nausea and vomiting. It is not clear that the delayed nausea and vomiting endpoints would have been reached if the comparison were made to these combination regimens.
4. Only chemotherapy regimens given on a single day were studied. Application of this antiemetic regimen to multiple-day chemotherapy regimens has potential risks due to possible drug-drug interactions with aprepitant.
5. Although the primary endpoint showed a statistically significant advantage over the standard therapy in all phases, the no nausea endpoint only reached statistical significance in one of the studies in the overall and delayed phase and the no significant nausea endpoint was only statistically significant in the acute phase. A complication to this analysis is that a higher percentage of patients in the standard group (27.6%) required rescue antiemetic therapy versus the aprepitant group (18%), which may affect the nausea scores.
6. Some chemotherapy drugs with high emetic potential (e.g. ifosfamide) were rarely studied and have the potential for a drug interaction.

7. Amifostine, which is used along with cisplatin, was excluded from use in this study, most likely because it causes nausea and vomiting. It is metabolized by p-glycoprotein and the drug interaction potential with aprepitant is unknown.
8. The use of aprepitant with radiation-induced nausea and vomiting has not been explored.
9. The use of aprepitant with other anti-emetic regimens has not been evaluated.

Acquisition Costs

Drug	Dose	Cost/Cycle /patient ($)	Cost/6 Cycles /patient ($)
Aprepitant	125mg(1) + 80mg (2)	182.45	1094.7
Ondansetron inj	32mg	72.24-91.53	433.44-549.18
Dexamethasone tab	4mg	0.56	3.36
Granistron tablet	1mg	19.24	115.44

Conclusions

Efficacy:
Aprepitant, when added to a standard antiemetic regimen that includes a $5HT_3$ antagonist and dexamethasone, followed by aprepitant for 2 days and dexamethasone for 3 days, is more effective than the standard regimen in preventing chemotherapy-induced vomiting in the acute and chronic phase for highly emetogenic chemotherapy that is administered on one day of the chemotherapy cycle. Its effects on acute and delayed nausea are not as clear-cut, although it has produced superior results in delayed nausea in some trials. There is no experience with chemotherapy regimens that are given over multiple days, or with some chemotherapy drugs that are highly emetogenic. Use of aprepitant for established nausea vomiting or for rescue therapy has not been studied.

Safety:
While the incidence of adverse events in cycle 1 was similar between the aprepitant group and the standard therapy group, there were increased incidences of adverse events, some serious, in the aprepitant group. The increased incidence of infections, neutropenia, and pulmonary toxicity may be the result of drug interactions.

Aprepitant is a substrate for and an inhibitor of CYP3A4. This fact increases the likelihood for a number of potential drug interactions. A small number of drug-drug interactions involving aprepitant and other CYP3A4 substrates have been identified. No drug interactions with chemotherapy drugs have been investigated, despite the fact that several are metabolized by CYP3A4 and could lead to serious adverse events. Although the registration study allowed for a multi-cycle extension of therapy, it is unclear how long-term use will affect the potential drug-drug interactions.

Cost:
Currently, the most expensive drugs for chemotherapy-induced nausea and vomiting are the $5HT_3$ antagonists. Attempts have been made to reduce the costs with this drug class, including use of oral therapy and reduced intravenous dose schedules. The addition of aprepitant to this standard regimen will more than double the cost for antiemetic therapy but can increase the quality of life by reducing vomiting and nausea and decreasing the costs for additional antiemetics for rescue therapy.

Recommendations

Aprepitant, when added to a regimen of a $5HT_3$ antagonist and dexamethasone as per the registration trial, is effective in reducing the incidence of chemotherapy-induced nausea and vomiting for highly emetogenic drugs, including cisplatin, given on one day of the chemotherapy cycle. Use of aprepitant with multiple-day chemotherapy regimens has not been investigated and is not generally part of a standard antiemetic protocol for these types of regimens. Use in radiation-induced nausea and vomiting has not been evaluated and caution should be exercised in this population. Drug-drug interactions with chemotherapy drugs have not been evaluated. Administration of aprepitant over multiple cycles should be closely monitored for potential drug interactions that could result in an increased incidence in adverse events. Aprepitant has not been evaluated for established or refractory nausea and vomiting. Use in these syndromes is generally not part of a standard protocol and would add significant costs.

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Prepared by: Mark C. Geraci, Pharm.D., BCOP
Date prepared: September 2003

<table>
<tr><th>Study</th><th>Inclusion/Exclusion</th><th>Drug Therapy</th><th>Characteristics</th><th>Results</th></tr>
<tr>
<td>Navari 1999
DB, R, MC, PC

Funded by Merck</td>
<td>1st course cisplatin ≥70mg/m^2</td>
<td>All groups:
D1 dex 20mg + gran 10mcg/kg

Grp 1:
D1 aprepitant 400mg
D2-5 aprepitant 300mg

Grp 2:
D1 aprepitant 400mg
D2-5 placebo

Grp 3:
D1 placebo
D2-5 placebo</td>
<td>
<table>
<tr><th></th><th>Daily</th><th>Single Dose</th><th>Placebo</th></tr>
<tr><td>No.</td><td>54</td><td>54</td><td>51</td></tr>
<tr><td>Male%</td><td>65</td><td>65</td><td>59</td></tr>
<tr><td>Age</td><td>64</td><td>61</td><td>60</td></tr>
<tr><td>N. of alcoholic drinks/wk (%)
0-4
5-10
≥11</td><td>
80
7
9</td><td>
87
7
4</td><td>
80
8
10</td></tr>
<tr><td>CDDP dose(mg/m^2)</td><td>77</td><td>80</td><td>81</td></tr>
<tr><td>Add. Emetogenic chemo (%)</td><td>4</td><td>4</td><td>4</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Outcome</th><th>Daily</th><th>Single Dose</th><th>Placebo</th></tr>
<tr><td>Episodes of Emesis
Acute (D1)
None (%)</td><td>93</td><td>94</td><td>67*</td></tr>
<tr><td>Delayed (d2-5)
None
1-2
≥3</td><td>
82
16
2</td><td>
78
15
7</td><td>
33*
26
41</td></tr>
<tr><td>Mean score on VAS (0-100) nausea
Acute
D2-5
D1-5</td><td>
0
1
1</td><td>
0
2
3</td><td>
1
5**
10**</td></tr>
</table>

*p<0.001 III vs I & II combined
**p=0.003 for comparison of grp 1 and grp 3

No significant differences in incidences of adverse events amount the three groups
</td>
</tr>
<tr>
<td>Campos 2001
DB, R, MC, PC

Funded by Merck</td>
<td>1st course cisplatin ≥70mg/m^2</td>
<td>Grp I
D -1: PB
D1: Gran 10mcg/kg
Dex 20mg
PB
D2-5: PB

Grp II
D -1: PB
D1: Gran 10mcg/kg
Dex 20mg
Aprepitant 400mg
D2-5: Aprepitant 300mg

Grp III
D -1: Aprepitant 400mg
D1: PB
Dex 20mg
Aprepitant 400mg
D2-5: Aprepitant 300mg

Grp IV
D -1: PB
D1: PB
Dex 20mg
Aprepitant 400mg
D2-5: Aprepitant 300mg</td>
<td>
<table>
<tr><th></th><th>I</th><th>II</th><th>III</th><th>IV</th></tr>
<tr><td>No.</td><td>90</td><td>86</td><td>89</td><td>86</td></tr>
<tr><td>Male%</td><td>58</td><td>58</td><td>61</td><td>60</td></tr>
<tr><td>Age</td><td>55</td><td>53</td><td>54</td><td>54</td></tr>
<tr><td>N. of Alcoholic Drinks/wk (%)
0-4
5-10
≥11</td><td>
84
6
10</td><td>
86
4
9</td><td>
83
7
10</td><td>
86
5
9</td></tr>
<tr><td>CDDP Dose mg/m^2</td><td>90</td><td>87</td><td>89</td><td>89</td></tr>
<tr><td>Add. Emetogenic Chemo %</td><td>24</td><td>27</td><td>24</td><td>21</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Outcome</th><th>I</th><th>II</th><th>III</th><th>IV</th></tr>
<tr><td>Episodes of emesis Acute
None %</td><td>57</td><td>80*</td><td>46</td><td>43</td></tr>
<tr><td>Delayed
None
1-2
≥3</td><td>
29
28
43</td><td>
63**
16
21</td><td>
51**
21
28</td><td>
57**
20
23</td></tr>
<tr><td>Mean score VAS Nausea
Acute
D2-5
D1-5</td><td>
7.5
7
7</td><td>
1*
2*
2*</td><td>
8.5
3†
3</td><td>
9.5
3
3</td></tr>
</table>
*p<0.01 for I vs II
**p<0.01 for I vs II, III, or IV
†p<0.05 versus group I

No significant differences in incidences of adverse events among groups, except for a higher incidence of diarrhea in groups III and IV (did not receive granisetron on day1).
</td>
</tr>
</table>

Van Belle 2001
DB, R, MC
Active control

Funded by Merck

1st course cisplatin ≥70mg/m²

Grp I
D1: L-758,298 100mg IV
Dex 20mg IV
D2-5: Aprepitant 300mg

Grp II
D1: L-758,298 100mg IV
Dex 20mg IV
D2-5: PB

Grp III
D1: Ondansetron 32mg IV
Dex 20mg IV
D2-5: PB

	I	II	III
No.	61	58	58
Male %	62	67	60
Age	59	56	59
No. of Alcoholic Drinks/wk (%)			
0-4	75	83	88
5-10	16	7	11
≥11	7	10	2
CDDP Dose mg/m²	90	87	88
Add. Emetogenic Chemo %	26	28	28

Outcome	I	II	III
Episodes of Emesis			
Acute			
None %	44	36	83*
Delayed			
None	65**	61**	41
1-2	19	17	17
≥3	15	21	41
Mean score VAS Nausea			
Acute	11	11	1†
D2-5	5	4	1
D1-5	5	6	1

*p<0.001 for III vs combined I & II
**p<0.05 for III vs I or II
† p<0.05 for III vs I, II or I+II

No significant differences in incidences of adverse events between groups except for a higher incidence of diarrhea in groups I and II (did not receive ondansetron).

Poli-Bigelli 2003
DB, R, MC, PC

1st course cisplatin ≥70mg/m²

Grp I:
D1: Ondansetron 32mg IV
Dex 20 mg
D2-4: Dex 8mg bid

Grp II:
D1: Aprepitant 125mg
Ondansetron 32mg IV
Dex 12mg
D2-3: Aprepitant 80mg
Dex 8mg
D4: Dex 8mg

	I	II
No.	286	283
Male%	51	52
Age	53	54
No. of alcoholic drinks/wk (%)		
0	87	84
1-10	12	14
>10	1	2
CDDP dose mg/m²	81	81
Add. Emetogenic Chemo %	17	17

Outcome	I	II
Episodes of emesis		
Acute		
None %	68.4	82.8*
Delayed		
None %	46.8	67.7*
Nausea		
Overall		
None %	39	49
Delayed		
None	40	53**

*P<0.001
**p<0.01

No significant differences in incidences of adverse events between groups.

<table>
<tr>
<td>De Wit R
2003
MC, R, DB, PC</td>
<td>1st course cisplatin ≥70mg/m^2
If appropriate, participation for up to 5 additional cycles</td>
<td>Grp I:
D1: Aprepitant 375mg
Ondansetron 32mg IV
Dexamethasone 20mg
D2-5: Aprepitant 250mg
Dex 8mg
(discontinued after 34 pts)

Grp II:
D1: Aprepitant 125mg
Ondansetron 32mg IV
Dexamethasone 20mg
D2-5: Aprepitant 80mg
Dex 8mg

Grp III:
D1: Placebo
Ondansetron 32mg IV
Dexamethasone 20mg
D2-5: Placebo
Dex 8mg</td>
<td>
<table>
<tr><td></td><td>I</td><td>II</td><td>III</td></tr>
<tr><td>No.</td><td>35</td><td>81</td><td>86</td></tr>
<tr><td>Male %</td><td>65.7</td><td>61.7</td><td>65.1</td></tr>
<tr><td>No. of alcoholic drinks/wk (%)
0
1-10
>10</td><td>

60
37.2
0</td><td>

63
25.9
11.1</td><td>

67.4
23.3
9.3</td></tr>
<tr><td>CDDP Dose mg/m^2</td><td>80.6</td><td>80.9</td><td>79.7</td></tr>
<tr><td>Add. Emetogenic therapy (%)</td><td>8.6</td><td>18.5</td><td>19.8</td></tr>
</table>
</td>
<td>
<table>
<tr><td>Outcome</td><td>I</td><td>II</td><td>III</td></tr>
<tr><td>Complete response
Cycle 1
Cycle 6</td><td>N/A</td><td>
64%
59</td><td>
49%*
34*</td></tr>
</table>
*p<0.05

Adverse events: (cycles 2-6) (%)
<table>
<tr><td></td><td>II</td><td>III</td></tr>
<tr><td>Drug-related AE</td><td>34</td><td>25</td></tr>
<tr><td>Serious AE</td><td>26</td><td>15</td></tr>
<tr><td>Serious drug-related AE</td><td>0</td><td>0</td></tr>
<tr><td>Discontinued due to AE</td><td>10</td><td>10</td></tr>
<tr><td>Most common AE:
Abd pain
Fatigue
Dehydration
Dizziness
Flu-like symptoms
Constipation
Diarrhea
Dysgeusia
Nausea
Anemia
Feb neutropenia
Headache
Hiccups
Dyspnea</td><td>
10
18
13
13
2
10
23
5
18
7
11
11
15
2</td><td>
10
17
10
10
2
13
13
7
13
13
2
15
8
5</td></tr>
</table>
</td>
</tr>
</table>

DB=double blind; R=randomized; MC=multicenter; PC=placebo controlled; dex=dexamethasone; gran =granisetron;PB=placebo