National PBM Drug Monograph
Aprepitant (Emend®)
August 2003; Updated September 2008
VA Pharmacy Benefits Management Services, VISN Formulary Leaders, 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 become 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 (CINV) and postoperative nausea and vomiting (PONV). 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 quaternised antagonist prevented cisplatin-induced emesis in ferrets when administered directly into the CNS but not when it was administered peripherally.

Table 1 Pharmacokinetics

Parameter	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

1. 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 high-dose cisplatin.

2. 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 moderately emetogenic chemotherapy.

2. Aprepitant is indicated for the prevention of postoperative nausea and vomiting.

Dosage and Administration[8,9]

Chemotherapy induced nausea and vomiting

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 regimens used in clinical trials is given below:

Table 2 Prevention of nausea and vomiting in highly emetogenic chemotherapy

Drug	Day1	Day 2	Day 3	Day 4
Aprepitant	125mg orally	80mg orally	80mg orally	none
Dexamethasone	12mg orally	8mg orally in am	8mg orally in am	8mg orally in am
Ondansetron	32mg IV	None	None	none

Table 3 Prevention of nausea and vomiting in moderately emetogenic chemotherapy

Drug	Day 1	Day 2	Day 3
Aprepitant	125mg orally	80mg orally	80mg orally
Dexamethasone	12mg orally	None	None
Ondansetron	8mg orally BID	None	none

Prevention of postoperative nausea and vomiting

Aprepitant 40mg orally within 3 hours prior to anesthesia induction.

Adverse Effects (Safety Data)

Table 4 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[10,11,12,13,14,15,16,17,18]

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. Metabolism of palonosetron *in vitro* suggests CYP2D6 and to a lesser extent 3A and 1A2 is involved in metabolism. Mean plasma-concentration curves for palonosetron administered with and without aprepitant are virtually identical. There is no pharmacokinetic data on oral ondansetron or IV granistron; there is no data with IV or oral dolasetron.

Chemotherapy agents: There is little 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- In a small pilot study of patients receiving cyclophosphamide plus thiotepa and carboplatin, aprepitant inhibited cyclophosphamide autoinduction by inhibiting CYP enzyme induction. However, this only resulted in a 7% higher cyclophosphamide exposure and a 5% lower exposure to 4-hydroxycyclophosphamide.

Docetaxel-Concomitant administration of aprepitant did not cause statistical or clinically relevant changes in docetaxel pharmacokinetics.
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.
Thiotepa- In a small pilot study (see cyclophosphamide above) aprepitant inhibited thiotepa metabolism resulting in a 20% lower tepa exposure.
Vinorelbine- In a small pilot study the mean plasma concentration curve of vinorelbine administered with aprepitant was equal to the plasma concentration curve of vinorelbine given alone.

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).
Flourouracil: 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 norethidrone 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. A trial in normal volunteers evaluated aprepitant 125mg orally on the AUC of IV midazolam. The geometric mean ratio for the AUC of aprepitant plus midazolam to midazolam alone was 1.47 (90%CI 1.36-1.59) showing aprepitant is a weak inhibitor of CYP3A4. 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 ketoconzole (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

Chemotherapy induced nausea and vomiting
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:
Table 5 Risk Factors for CINV

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

Postoperative nausea and vomiting
Primary Endpoints:
No emesis- no emetic episodes in the 0-24 hours following the end of surgery
Complete Response- no emetic episodes and no use of rescue therapy for established nausea and vomiting in the 0-24 hours following the end of surgery.

Secondary Endpoints:
No emesis in the 0-48 hours following the end of surgery.
Time to first emesis in the 0-48 hours following the end of surgery.
Time to first use of rescue therapy in the 0-24 hours following the end of surgery.

Clinical Trials[7,19,22,]

Prevention of CINV in patients receiving highly-emetogenic chemotherapy
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). A third trial evaluated efficacy over multiple cycles of highly-emetogenic chemotherapy.

Table 6 Efficacy in Highly-Emetogenic Chemotherapy

Inclusion/Exclusion	Dose	Patient Characteristics	Results
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	<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	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	See table below

	Aprep %	Standard %
Complete Response (no V , no rescue)		
Study 052		
Overall phase	72.7**	52.3
Acute phase	89.2**	78.1
Delayed phase	75.4**	55.8
Study 054		
Overall phase	62.7**	43.3
Acute phase	82.8**	68.4
Delayed phase	67.7**	46.8
No Nausea (max <5 mm on VAS)		
Study 052		
Overall phase	47.5	44.2
Acute phase	72.3	69.1
Delayed phase	51.0	47.7
Study 054		
Overall phase	48.8*	38.8
Acute phase	67.7	66.2
Delayed phase	52.7**	39.9
No significant nausea (max <25 mm on VAS)		
Study 052		
Overall phase	73.2	66.0
Acute phase	91.0	86.5
Delayed phase	75.3	68.5
Study 054		
Overall phase	71.1	63.9
Acute phase	90.4*	82.3
Delayed phase	72.7	65.4
Complete protection (no V, no rescue, no significant nausea (VAS<25 mm) Aprepitant group statistically significantly better than standard group in all phases		
Time to First Emesis Kaplan-Meier curves show time to first emesis was longer in the aprepitant group starting 16 hours after cisplatin administration		
Multiple-cycle extension Time to First Emesis curves show aprepitant group maintained superiority over standard therapy group		

**p<0.01 *p<0.05

<table>
<tr>
<td>de Wit, et al.[20]
Extension trial for multiple cycles

Inclusion
1. Cisplatin naïve patients
2. Cisplatin ≥70 mg/m^2
3. Karnofsky ≥60</td>
<td><u>Aprepitant:</u>
Aprepitant 125mg D1
Dex 20 mg IV D1
Ond 32mg IV D1

Aprepitant 80mg D2-5
Dex 8mg qam D2-5
PCB qpm D2-5

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

Aprep PCB D2-3
Dex 8mg qam D2-5
Dex 8mg qpm D2-5

(A third group received aprepitant 325mg day 1 and aprepitant 250mg days 2-5 but was discontinued due to pharmacokinetic data from other trials showed higher than expected aprepitant plasma levels in combination with dexamethasone)</td>
<td>N=202
% Male: 62-66
Age: 58
Cisplatin Dose:
<100/m^2-91-93%
≥100/m^2-6-7%
Alcohol
Drinks per week
0- 60-67%
1-10 23-37%
>10 0-11%</td>
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<tr><td>Therapy</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
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<tr><td>#withdraw</td><td>0</td><td>34</td><td>9</td><td>15</td><td>8</td><td>3</td></tr>
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<tr><td>#withdraw</td><td>0</td><td>46</td><td>13</td><td>10</td><td>4</td><td>4</td></tr>
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P<0.05 for Cycles 1, 5, 6 for estimated probability of complete response of aprepitant plus standard therapy versus standard therapy alone
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PCB=placebo, CR=complete response; PR=partial response

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.

There are relatively few trials looking at antiemetic efficacy over multiple cycles. Response rates were similar in the aprepitant group over 6 cycles while the efficacy with standard therapy diminished over time as has been observed in other clinical trials.

Adverse events over multiple cycles of chemotherapy were generally similar across treatment groups. There were a higher number of serious adverse events in the aprepitant group, primarily due to a greater number of patients with febrile neutropenia and various infection-related events. This may be due to the pharmacokinetic interaction with dexamethasone; subsequent trials utilized a lower modified dose.

Pooled Analysis[21,2223]

In attempts to further characterize the data from these 2 registration trials, several data points were analyzed using pooled data.

Gralla, et al. examined the benefits of aprepitant in patients at greater risk for CINV due to combinations of emetogenic chemotherapy in addition to cisplatin. Cyclophosphamide and doxorubicin were the two most emetogenic agents and the focus of the analysis. In 142 patients receiving doxorubicin and/or cyclophosphamide in addition to cisplatin, aprepitant was superior to standard therapy (59% vx 26%; p<0.001). In addition, aprepitant produced higher rates of response in both the acute (71% vs 49%) and delayed phases (67% vs 32%) (p<0.05 for both).

Warr, et al. analyzed the pooled data to determine if the results in the first 24 hours (acute control) predict the results in the delayed phase. Complete response in the acute phase (86% vs 73%; p<0.001) and delayed phase (72% vs 51%; p<0.001) were superior for the aprepitant groups. Delayed emesis was more frequent in those that experienced acute emesis regardless of the treatment group.

Finally, Hesketh, et al. assessed the impact of aprepitant on CINV prevention in female patients, as female gender is a recognized risk factor for CINV. Complete responses were higher in males compared to females (61% vs 53%) regardless of the treatment group. This difference held true in all three time periods evaluated (D1-5, D1, D2-5). Within each gender, the aprepitant group was superior to the standard therapy group in response rates. In patients who opted to continue beyond cycle 1, time to first emesis was plotted on a Kaplan-Meier curve. Aprepitant provided a higher rate of protection regardless of gender. Males had slightly higher response rates over the six cycles.

Delayed CINV in Highly-Emetogenic Chemotherapy

Table 7 Delayed CINV in Highly-Emetogenic Chemotherapy

Inclusion/Exclusion	Dose	Patient Characteristics	Results
Schmol et al.[24] Inclusion: 1. Cisplatin naïve 2. Cisplatin ≥70 mg/m^s 3. Karnofsky ≥60 Exlusion: 1. Stem cell rescue 2.Multiple day cisplatin 3.5HT3 w/I 48 hours 4. XRT to abdomen or pelvis 1 wk before up to D6 5. Symptomatic CNS tumor 6. Active infection 7. vomiting or dry heaves 24hrs before treatment	Aprepitant Aprepitant 125mg po D1 Ondansetron 32mg IV D1 Dexamethasone 12mg D1 Aprepitant 80mg D2-3 Dexamethasone 8mg D2-4 Placebo in evening D2-4 Ondansetron placebo BID D2-4 Standard Aprepitant placebo D1 Ondansetron 32mg IV D1 Dexamethasone 20mg D1 Aprepitant placebo D2-3 Ondansetron 8mg BID D2-4 Dexamethasone 8mg BID D2-4	N=489 %Male: 61-65 Age: 58-59 Cisplatin dose 70 to <100/m^2 74-75% Alcohol Drinks per week 0 67-71% 1-7 18-23 >7 11 H/o Motion sickness 5-6% CINV 4-6%	

Outcome	Aprep	Stand	OR 95%CI	P-value
CR				
0-120	72	60.6	1.8 1.21-2.66	0.003
0-24	87.7	79.3	2.1 1.25-3.57	0.005
>24-120	74	63.1	1.78 1.2-2.65	0.004
No vomit				
0-120	76.5	62.2	2.14 1.43-3.22	≤0.001
0-24	88.9	80.5	2.17 1.27-3.69	0.004
>24-120	7.9	64.3	2.24 1.48-3.40	≤0.001
No rescue				
0-120	82.3	79.7	1.23 0.78-1.96	0.373
0-24	94.2	92.9	1.32 0.63-2.77	0.468

			>24-120	83.5	81.7	1.17 0.73-1.88	0.517
			No sign nausea				
			0-120	73.1	69.7	1.24 0.83-1.87	0.290
			0-24	92.1	89.5	1.45 0.77-2.76	0.254
			>24-120	75.9	72.1	1.28 0.84-1.94	0.248

CINV=chemotherapy-induced nausea and vomiting; CR=complete response; sign=significant; OR=odds ratio

Prevention of CINV in patients receiving moderately-emetogenic chemotherapy

Table 8 Prevention of CINV in Moderately-Emetogenic Chemotherapy

Inclusion/Exclusion	Dose	Patient Characteristics	Results
Warr, et al.[25] Inclusion 1. Breast CA 2. Naïve to emetogenic chemotherapy 3.Karnofsky ≥60 4. Chemo Cyclophos 750-1500/m^2 IV Cyclophos 500-1500 + Doxorubicin ≤60mg/m^2 Cyclophos 500-1500 + Epirubicin ≤100mg/m^2 Exclusion 1. Symptomatic CNS malignancy 2. XRT to abdomen or pelvis week before treatment 3. taking corticosteroids 4. vomiting 24 hrs before D1 5. Active infection	Aprepitant (n=438) Aprepitant 125mg po D1 Ondansetron 8mg BID D1 Dexamethasone 12mg D1 Aprepitant 80mg po D2-3 Standard Ondansetron 8mg BID D1 Dexamethasone 20mg D1 Ondansetron 8mg BID D2-3	% female: 99.8 Age: 52-53 %white: 77.6-79.9 h/o motion sickness: 17-21% Vomiting/ pregnancy 31% Cyclo + dox: 61% Cyclo +epi+5FU: 21%	Outcome / Aprep / Standard / P-value CR 0-120: 51 / 42 / 0.015 0-24: 76 / 69 / 0.034 >24-120: 55 / 49 / 0.064 No vomiting 0-120: 76 / 59 / <0.001 0-24: 88 / 77 / <0.001 >24-120: 81 / 69 / <0.001 No differences between groups in use of rescue medications
Herrstedt et al.[26] (continuation of Warr et al. in subsequent cycles)			1 / 2 / 3 / 4 / P CR: A 50.8 / 40.9 / 37.9 / 34.5; S 42.5 / 30.7 / 26.3 / 23.9; P 0.017 No V: A 75.7 / 70.4 / 66.8 / 62.9; S 58.7 / 47.6 / 42.3 / 38.8; P <0.001

CR=complete response; Cyclo=cyclophosphamide; dox=doxorubicin; epi=epirubicin; 5FU=5-flourouracil; V=vomiting;A=aprepitant; S=standard

Prevention of postoperative nausea and vomiting

Table 9Prevention of PONV

Inclusion/Exclusion	Dose	Patient Characteristics	Results
Diemunsch et al.[27] Inclusion 1. Abdominal surgery with overnite stay 2. volatile agent based anaesthesia Exclusion 1. Pregnancy/breast feeding 2. neuoroaxial or propofol anaesthesia 3. allergy to any medication used pre-op or intraoperatively	Aprepitant 40mg po Or Aprepitant 80mg po Or Ondansetron 4mg IV Non-inferiority trial for complete response Superiority trial for no vomiting	N=922 Age:46 %white: 50 %African-American: 9-13 % Hispanic: 16-17 %Asian: 10-11 Anaesth duration 1.8-2 hrs h/o PONV: 13-18% # risk factors for PONV 0 0.3-0.4% 1 5-6 2 23-27 3 50-54	A40 / A125 / Ond CR: 64% / 63% / 55% OR: 1.4 / 1.4 95%CI Lower bound: 1.08 / 1.04 No V: 82% / 85% / 66% OR: 2.1 / 2.8 P: <0.001 / <0.001

<table>
<tr>
<td>4.vomiting within 24 hours before surgery
5. pre-established need for ICU or step-down care
6. meds known to induce CYP3A4 within previous 30 days
7.CYP3A4 substrates or inhibitors within 7 days</td>
<td></td>
<td>4 14-19</td>
<td></td>
</tr>
<tr>
<td>Gan et al.[28]
Inclusion
1. Abdominal surgery with overnite stay
2.volatile-agent based anaesthesia

Exclusion
1. surgery requiring routine replacement of NG or OG tube
2. pregnancy/breast feeding
3. spinal/regional or propofol anaesthesia
4. vomiting within past 24 hours
5. Meds metabolized by CYP3A4 with narrow therapeutic window</td>
<td>Aprepitant 40mg po
Or
Aprepitant 125mg po
Or
Ondansetron 4mg IV</td>
<td>N=766
Age:44-46
Female: 94-95%
%white: 64-71
%Afr-American: 17-25
%Asian: 1-2

# of risk factors for PONV
0 0-0.4%
1 2-3
2 22-24
3 42-46
4 27-32</td>
<td>
<table>
<tr><th></th><th>% responding</th><th>OR</th><th>P value</th></tr>
<tr><td>CR
Aprep40
Ondan</td><td>
44.8
42.3</td><td>1.1</td><td>0.4</td></tr>
<tr><td>No V 0-24hrs
Aprep40
Ondan</td><td>
89.9
73.6</td><td>3.2</td><td><0.001</td></tr>
<tr><td>No V 0-48 hrs
Aprep40
Ondan</td><td>
84.6
66.9</td><td>2.7</td><td><0.001</td></tr>
</table>
There was no difference in efficacy rates between aprepitant 40mg and apreptitant 125mg
</td>
</tr>
</table>

CR=complete response; OR=odds ratio; V=vomiting; h/o=history of; PONV=postoperative nausea and vomiting

Combined Analysis[29]

Diemunsch, et al. performed a pooled analysis of the two trials in PONV. In the 24 hours after surgery, aprepitant 40mg was superior to ondansetron for all 5 endpoints tested:
1) No Significant nausea (56.4% vs48.1%) OR 1.4 p=0.009
2) No Nausea (39.6% vs 33.1%) OR 1.3 p=0.035
3) No Vomiting (86.7% vs 72.4%) OR 2.5 p<0.001
4) No Nausea or No Vomiting (38.3% vs 31.4%) OR 1.3 p=0.023
5) No Nausea, No Vomiting, No Rescue Medications (37.9% vs 31.2%) OR 1.3 p=0.027

Supporting Trials: (see attachment) [2,30,31,32,33,34]

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 in the registration trials and a potential drug interaction resulting in higher ondansetron

concentrations is expected. This was not borne out in subsequent studies using lower doses of oral ondansetron. 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.
10. The use of aprepitant in multiple day chemotherapy cycles has not been established.

Acquisition Costs (as of 9/08)

Drug	Dose	Cost/Cycle /patient ($)	Cost/6 Cycles /patient ($)
Aprepitant	125mg(1) + 80mg (2)	109.16-207.91	654.96-1247.46
Ondansetron inj	32mg	3.78-6.17	22.68-37.02
Dexamethasone tab	4mg	0.56	3.36

Cost-effectiveness studies[35,36,37]

Moore, et al. developed a Markov model to compare costs and outcomes of patients receiving highly emetogenic chemotherapy. Costs were calculated from the payors perspective. Utilities were measured in healthy day equivalents (HDE's) and converted to quality adjusted life-years (QALY's) to calculate incremental benefits. Aprepitant as part of a 3 drug regimen, provides 2.47 additional HDE's at a cost of $682. Adding aprepitant only after CINV developed added an additional 1.24HDE's at a cost of $289. The incremental cost effectiveness ratios were $97,429/QALY for the 3 drug regimen and $96,333/QALY for the addition of aprepitant only after CINV began.

Lordick, et al. examined health outcomes and cost-effectiveness for highly emetogenic chemotherapy in Germany by developing a decision analytic model to compare aprepitant with a control regimen. The cost-effectiveness of aprepitant was calculated at €28,891 per QALY.

Annemans, et al. explored the cost-effectiveness of aprepitant versus standard prevention for CINV in Belgium using a decision tree model. For highly emetogenic chemotherapy, aprepitant is associated with 0.003 more QALY and a per patient cost savings of €66.84-74.62. For moderately emetogenic chemotherapy, the gain in QALY is 0.014 with a per patient cost saving of €17.95 – 21.70.

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 pooled data. There is no experience with chemotherapy regimens that are given over multiple days, or with chemotherapy drugs other than cisplatin that are highly emetogenic. Use of aprepitant for established nausea vomiting or for rescue therapy has not been studied.

Aprepitant also has activity in moderately emetogenic chemotherapy versus a standard regimen. Again, the benefits are driven by the prevention of vomiting episodes versus nausea.

In the postoperative studies, aprepitant was non-inferior to a standard ondansetron dose with regard to complete response over 24 hours post surgery. When evaluating vomiting episodes in the 48 hour period following surgery, aprepitant was superior to ondansetron for response rate. Pooled data analysis found aprepitant superior in preventing nausea, vomiting, and use of rescue medications versus ondansetron.

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 drug for chemotherapy-induced nausea and vomiting is aprepitant since the generic version of ondansetron became available in 2007. The addition of aprepitant to this standard regimen increases the cost for antiemetic therapy more than 30 times 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. The routine use of a 3 drug regimen, including aprepitant, with the first and subsequent

doses of any highly-emetogenic chemotherapy regimen is endorsed by the most recent guidelines from the American Society of Clinical Oncology (ASCO)[38], the Multinational Association of Supportive Care in Cancer (MASCC) consensus proposol[39] and the European Medicines Agency (EMEA) considered the risk/benefit profile for aprepitant for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin based therapy as part of a combination regiment to be favorable and recommended the granting of marketing authorization. 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. The use of aprepitant in moderately emetogenic regimens should be reserved for the combination of cyclophosphamide and doxorubicin or cyclophosphamide plus epirubicin as commonly used in breast cancer. 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. Use of aprepitant in place of ondansetron in PONV is a more difficult decision, especially when looking at cost. It would seem prudent to limit its use to patients with the highest risk for the development of PONV.

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September 2003; Updated September 2008.

<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>

<table>
<tr>
<td>Van Belle 2001
DB, R, MC
Active control

Funded by Merck</td>
<td>1st course cisplatin ≥70mg/m^2</td>
<td>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</td>
<td>
<table>
<tr><th></th><th>I</th><th>II</th><th>III</th></tr>
<tr><td>No.</td><td>61</td><td>58</td><td>58</td></tr>
<tr><td>Male %</td><td>62</td><td>67</td><td>60</td></tr>
<tr><td>Age</td><td>59</td><td>56</td><td>59</td></tr>
<tr><td>No. of Alcoholic Drinks/wk (%)
0-4
5-10
≥11</td><td>
75
16
7</td><td>
83
7
10</td><td>
88
11
2</td></tr>
<tr><td>CDDP Dose mg/m^2</td><td>90</td><td>87</td><td>88</td></tr>
<tr><td>Add. Emetogenic Chemo %</td><td>26</td><td>28</td><td>28</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Outcome</th><th>I</th><th>II</th><th>III</th></tr>
<tr><td>Episodes of Emesis
Acute
None %

Delayed
None
1-2
≥3</td><td>
44

65**
19
15</td><td>
36

61**
17
21</td><td>
83*

41
17
41</td></tr>
<tr><td>Mean score VAS Nausea
Acute
D2-5
D1-5</td><td>
11
5
5</td><td>
11
4
6</td><td>
1†
1
1</td></tr>
</table>
*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).
</td>
</tr>
<tr>
<td>Poli-Bigelli 2003
DB, R, MC, PC</td>
<td>1st course cisplatin ≥70mg/m^2</td>
<td>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</td>
<td>
<table>
<tr><th></th><th>I</th><th>II</th></tr>
<tr><td>No.</td><td>286</td><td>283</td></tr>
<tr><td>Male%</td><td>51</td><td>52</td></tr>
<tr><td>Age</td><td>53</td><td>54</td></tr>
<tr><td>No. of alcoholic drinks/wk (%)
0
1-10
>10</td><td>
87
12
1</td><td>
84
14
2</td></tr>
<tr><td>CDDP dose mg/m^2</td><td>81</td><td>81</td></tr>
<tr><td>Add. Emetogenic Chemo %</td><td>17</td><td>17</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Outcome</th><th>I</th><th>II</th></tr>
<tr><td>Episodes of emesis
Acute
None %

Delayed
None %</td><td>

68.4

46.8</td><td>

82.8*

67.7*</td></tr>
<tr><td>Nausea
Overall
None %

Delayed
None</td><td>

39

40</td><td>

49

53**</td></tr>
</table>
*P<0.001
**p<0.01

No significant differences in incidences of adverse events between groups.
</td>
</tr>
</table>

De Wit R 2003 MC, R, DB, PC	1st course cisplatin ≥70mg/m^2 If appropriate, participation for up to 5 additional cycles	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		I	II	III			
			No.	35	81	86			
			Male %	65.7	61.7	65.1			
			No. of alcoholic drinks/wk (%) 0 1-10 >10	 60 37.2 0	 63 25.9 11.1	 67.4 23.3 9.3			
			CDDP Dose mg/m^2	80.6	80.9	79.7			
			Add. Emetogenic therapy (%)	8.6	18.5	19.8			
			Outcome	I	II	III			
			Complete response Cycle 1 Cycle 6	N/A 	 64% 59	 49%* 34*			
			*p<0.05						
			Adverse events: (cycles 2-6) (%)						
				II	III				
			Drug-related AE	34	25				
			Serious AE	26	15				
			Serious drug-related AE	0	0				
			Discontinued due to AE	10	10				
			Most common AE: Abd pain Fatigue Dehydration Dizziness Flu-like symptoms Constipation Diarrhea Dysgeusia Nausea Anemia Feb neutropenia Headache Hiccups Dyspnea	 10 18 13 13 2 10 23 5 18 7 11 11 15 2	 10 17 10 10 2 13 13 7 13 13 2 15 8 5			

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