

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Aprepitant (Emend™) Prevention of Postoperative Nausea and Vomiting
8/2006

Recommendations:

- Aprepitant (Emend™) is not recommended for formulary inclusion for prevention of postoperative nausea and vomiting (PONV). The multiple center study conducted in the U.S. failed to demonstrate a statistically significant difference between aprepitant 40 mg oral and a single dose of ondansetron 4 mg injection.
 - Zofran administration was not timed appropriately in the studies
 - Agents from multiple classes may be combined for patients at high risk of PONV (dexamethasone, 5HT3 receptor antagonists, droperidol, prochlorperazine) to reduce the risk of PONV at a lower cost with a high efficacy rate.
 - Coadministration of aprepitant with warfarin may significantly decrease INR for those patients on chronic warfarin therapy. Monitor closely in the two week period (*particularly at 7-10 days*) following both the 3 day chemotherapy regimen and the one time 40 mg dose of aprepitant.
 - Patients using oral contraceptives require an alternative method for one month following aprepitant.
 - The **Antiemetic Prophylaxis For Patients At Risk For PONV** card will be made available to the anesthesia groups to help promote a more systematic approach.

Cost Comparison		
Medication	Cost	340B Cost
Zofran 4mg/2ml*	\$16.61	\$10.46
Kytril 0.1 mg	\$9.29	\$4.06
Prochlorperazine 10mg	\$1.47	\$1.76
Promethazine 25mg	\$0.63	\$0.58
Dexamethasone 10mg	\$1.13	\$0.98
Emend 40 mg	\$37.58	\$38.74
Droperidol 0.625 mg	\$0.92	

***Zofran is expected to become available in the generic form on 12/06.**

Findings:

- Indication: Prevention of postoperative nausea and vomiting (PONV)
- Recommended dose of Emend for PONV is a single, oral 40 mg dose administered within 3 hours prior to beginning anesthesia. A higher dose of 125 mg does not provide any additional benefit.
- Risk Factors for PONV:
 - Female, history of PONV/motion sickness, opioid therapy, non-smoker

Number of Risk Factors	Risk Classification	Incidence of PONV	Recommended Prophylaxis
0-1	Low	10-21%	NONE or one agent
2-3	Moderate	39-60%	One or Two agents
3-4	High	61-79%	Three or more agents

First Line Agents (dexamethasone, droperidol, 5HT3 antagonist) reduce incidence of PONV by approximately 26%. When first line agents are combined, the same % reduction is produced by each additional agent administered. N Engl J Med. 2004 Jun 10; 350 (24): 2441-51.

- Contraindications:
 - Aprepitant should not be used with pimozone, terfenadine, astemizole, or cisapride because of inhibition of cytochrome P450 3A4 by aprepitant.
- Precautions:
 - Use with caution in patients who are receiving any medications that are primarily metabolized through CYP3A4. Weak inhibition with 40 mg dose.
 - Co-administration with hormonal contraceptives may reduce the efficacy of the contraceptives, therefore a back-up method of contraception should be used during and for 1 month after using aprepitant.

	Aprepitant	Ondansetron
Mechanism of Action	High affinity antagonist of human substance P/neurokinin 1 (NK1) receptors	5HT3 receptor antagonist
Half Life	9-13 hours	3-6 hours
Metabolism	Major: CYP3A4 Minor: CYP1A2, CYP2C19	Major: CYP3A4 Minor: CYP1A2, CYP2C9, CYP2D6, CYP2E1
CYP450 Inhibition	Moderate: CYP3A4 Weak: CYP2C9, CYP2C19	Weak: CYP1A2, CYP2C9, CYP2D6
CYP450 Induction	Weak: CYP2C9, CYP3A4	None
Indication	Prevention of post operative nausea and vomiting	Prevention and treatment (if no prophylactic dose received) of postoperative nausea and/or vomiting
Dosage	40 mg PO within 3 hours before anesthesia	4 mg IV in not less than 30 seconds, pref. over 2-5 min. approximately 15 minutes before the end of surgery OR 16 mg PO 1 hour prior to induction of anesthesia
Protein Bound	95%	70% - 76%
Renal Adjustment	Not renally excreted therefore no adjustment necessary	No reduction in dose or dosing frequency needed
Hepatic Adjustment	No dosage adjustment needed for mild to moderate insufficiency (Child-Pugh Score of 5-9). No data is available for severe insufficiency (Child-Pugh Score >9)	Severe hepatic impairment, total daily dose of 8 mg should not be exceeded

DRUG INTERACTIONS WITH APREPITANT IN CHEMOTHERAPY PROPHYLAXIS AND PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING

	Drugs	Interactions	Action
CYP3A4 Inhibitors	Ketoconazole, Itraconazole, Nefazodone, Troleandomycin, Clarithromycin, Ritonavir, Nelfinavir, or Diltiazem	Increased plasma Concentrations of aprepitant ≥ 2 fold	Approach with caution.
CYP3A4 Inducers	Rifampin, Carbamazepine, or Phenytoin	Decreased plasma Concentrations of aprepitant-	Monitor efficacy.
	Paroxetine	Decrease in AUC of Aprepitant and paroxetine.	Consider when co-administration is necessary.
CYP3A4 Substrate (Aprepitant Inhibits Metabolism)	Dexamethasone	Increases AUC of Dexamethasone	Decrease oral Dexamethasone dose by 50% when co-administered w/Aprepitant; No dosage adjustment necessary after single 40 mg dose.
	Pimozide, Terfenadine, Astemizole, or Cisapride	Elevated plasma Concentrations	Do not use Aprepitant concurrently with these medications.
	Etoposide, Vinorelbine, or Paclitaxel	Elevated plasma Concentrations	It was used in a small # of pts in a study with no dosage adjustment done, however caution and careful monitoring are advised.
	Vinblastine, vincristine, ifosfamide, or other chemotherapy agents metabolized primarily by CYP3A4	Elevated plasma Concentrations	Use caution and monitor carefully
	Midazolam and other Benzodiazepines metabolized Via CYP3A4 such as Alprazolam and Triazolam	Increased plasma Concentrations	Use alternative agent. Midazolam 2 mg po coadministered with aprepitant 40 mg on the same day was found to increase the AUC of midazolam to non clinically important levels
	Methylprednisolone	Increased AUC of Methylprednisolone	Reduce the IV dosage by 25% and the oral dosage by 50% when administered with Aprepitant. No dosage adjustment necessary after single 40 mg dose.
	Oral Contraceptives	Decreased efficacy	Make sure to use alternative or backup methods during aprepitant therapy and for one month following the last dose.
CYP2C9 Substrate	Warfarin	Decreased INR, decrease concentrations of warfarin	Monitor INR readings for 2 weeks especially on days 7-10 following initiation of the 3 day regimen of Emend w/ each chemo cycle and following single 40 mg PONV dose.
	Tolbutamide, Phenytoin	Decreased plasma Concentrations	Monitor plasma levels, blood sugar or symptom profile.

See the PI for more complete details.

Per PI: *A single dose of aprepitant is not expected to alter plasma concentrations of drugs that are primarily metabolized through CYP3A4 to a clinically significant degree. Also, the effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect on drugs administered intravenously.*

Adverse Reactions (Summarized in Table 9):

- Manufacturer claims that aprepitant was generally well tolerated and that the adverse effects reported in the two studies were mild to moderate in intensity
- Also claim there were no serious adverse effects reported in the PONV studies in patients that received 40 mg aprepitant
- Approximately 60% of patients that received aprepitant 40 mg experienced an adverse effect believed to be caused by the drug compared to 64% for those that received Ondansetron 4 mg IV.

Table 9**Percent of Patients Receiving General Anesthesia With Clinical Adverse Experiences (Incidence $\geq 3\%$)**

	Aprepitant 40 mg (N=564)	Ondansetron (N=538)
<i>Infections and Infestations</i>		
Urinary Tract Infection	2.3	3.2
<i>Blood and Lymphatic System Disorders</i>		
Anemia	3.0	4.3
<i>Psychiatric Disorders</i>		
Insomnia	2.1	3.3
<i>Nervous System Disorders</i>		
Headache	5.0	6.5
<i>Cardiac Disorders</i>		
Bradycardia	4.4	3.9
<i>Vascular Disorders</i>		
Hypertension	2.1	3.2
Hypotension	5.7	4.6
<i>Gastrointestinal Disorders</i>		
Constipation	8.5	7.6
Flatulence	4.1	5.8
Nausea	8.5	8.6
Vomiting	2.5	3.9
<i>Skin and Subcutaneous Tissue Disorders</i>		
Pruritus	7.6	8.4
<i>General Disorders and General Administration Site Conditions</i>		
Pyrexia	5.9	10.6

Note: Aprepitant 40 mg PO was compared to Ondansetron 4 mg IV in Table 9

PONV study 1 and 2 from Package Insert:

- Two multicenter, randomized, double-blind, active comparator-controlled parallel group clinical studies involving 1658 patients undergoing open abdominal surgery
- Patients randomly received either 40 mg aprepitant PO, 125 mg aprepitant PO, or 4 mg ondansetron IV.
- Aprepitant was given orally 1-3 hours pre-anesthesia
- Ondansetron was given intravenously immediately before anesthesia (however, current recommendations state ondansetron should be given 15 minutes prior to the end of surgery).
- There is no significant difference between the 125 mg and 40 mg dose of aprepitant therefore the results that were analyzed compared the 40 mg dose to Ondansetron 4 mg IV in both studies.
- Study population: 92 % female, 8% male. 58% white, 14% African American, 13% Hispanic American, 7% Multi-racial, 6% Asian, 2% Other, Age ranged from 19 to 84 years, mean age 46.1
- Most patients had 3-4 risk factors for PONV with distribution similar across treatment groups (non-smoker, female, H/O PONV/motion sickness, and use of postoperative opioids).
- Antiemetic activity was followed for 48 hours post surgery
- PONV Study 1 was multinational including the U.S., PONV Study 2 was only conducted in the U.S.
- Of the patients receiving aprepitant 40 mg in PONV study 1, 81% underwent gynecological surgeries and 19% underwent non-gynecological surgeries. Of the patients receiving Ondansetron 4 mg in PONV study 1, 83% underwent gynecological surgeries and 17% underwent non-gynecological studies
- Of the patients receiving aprepitant 40 mg in PONV study 2, 92% underwent gynecological surgeries and 8% underwent non-gynecological surgeries. Of the patients receiving Ondansetron 4 mg in PONV study 2, 91% underwent gynecological surgeries and 9% underwent non-gynecological surgeries.
- According to Merck, the manuscripts for the two PONV studies are currently in the process of being written with the intent to publish.

Inclusion Criteria

- At least 18 years of age
- Having an American Society of Anesthesiologists physical status of I-III
- Scheduled to receive general balanced anesthesia (including nitrous oxide with volatile anesthetics)
- Open abdominal surgery that required at least a 24 hour stay in the hospital following the end of surgery.
- Surgeries performed included hysterectomy + salpingo-oophorectomy, hysterectomy, salpingo-oophorectomy, myomectomy, prostatectomy, intestinal resection, hernia repair, cholecystectomy, nephrectomy, laparotomy, and bladder surgery.

Exclusion Criteria

- Pregnant or breast-feeding
- Surgery requiring routine placement of a nasogastric tube or oral-gastric tube
- Spinal regional or propofol-maintained anesthesia (propofol was permitted for induction of anesthesia)
- Vomiting of any organic etiology
- Vomiting for any reason within 24 hours of surgery or abnormal laboratory values as specified by the protocol (abnormal laboratory values were undefined)
- Receiving opioid antagonists or benzodiazepines
- Receiving CYP3A4 substrates terfenadine, cisapride, astemizole, or pimozide within 7 days of surgery
- Receiving CYP3A4 inducers phenytoin, carbamazepine, barbiturates, rifampicin, or rifabutin within 30 days of surgery
- Receiving CYP3A4 inhibitors clarithromycin, ketoconazole, or itraconazole within 7 days of surgery
- Participated in a previous aprepitant study
- Had taken an investigational drug within the previous 4 weeks

Limitations of PONV Studies:

- Patients were not allowed any other prophylactic antiemetics within 24 hours preoperatively, intraoperatively, or postoperatively.
- Patients could also only request and receive rescue antiemetics if he/she had more than 1 episode of vomiting or retching or if the patient had nausea lasting longer than 15 minutes.
- The duration of the surgeries is not provided.
- The administration of Ondansetron was done immediately before anesthesia, which according to the **Consensus Guidelines for Managing Postoperative Nausea and Vomiting** by Gan et al. is not the optimal time to administer the drug. The guidelines recommend administration of Ondansetron at the end of surgery.

Efficacy measures in PONV Study 1 include:

- No emesis (no emetic episodes regardless of use of rescue therapy) in the first 24 hours following the end of surgery (Primary Endpoint)
- Complete response (No emesis and no rescue therapy) in the first 24 hours following surgery (Primary Endpoint)
- No emesis (no emetic episodes regardless of use of rescue therapy) in the first 48 hours following surgery (Secondary Endpoint)
- Time to first emesis in the 0 to 48 hours following the end of surgery (Exploratory Endpoint)
- Time to first use of rescue therapy in the 0 to 24 hours following the end of surgery (Exploratory Endpoint)

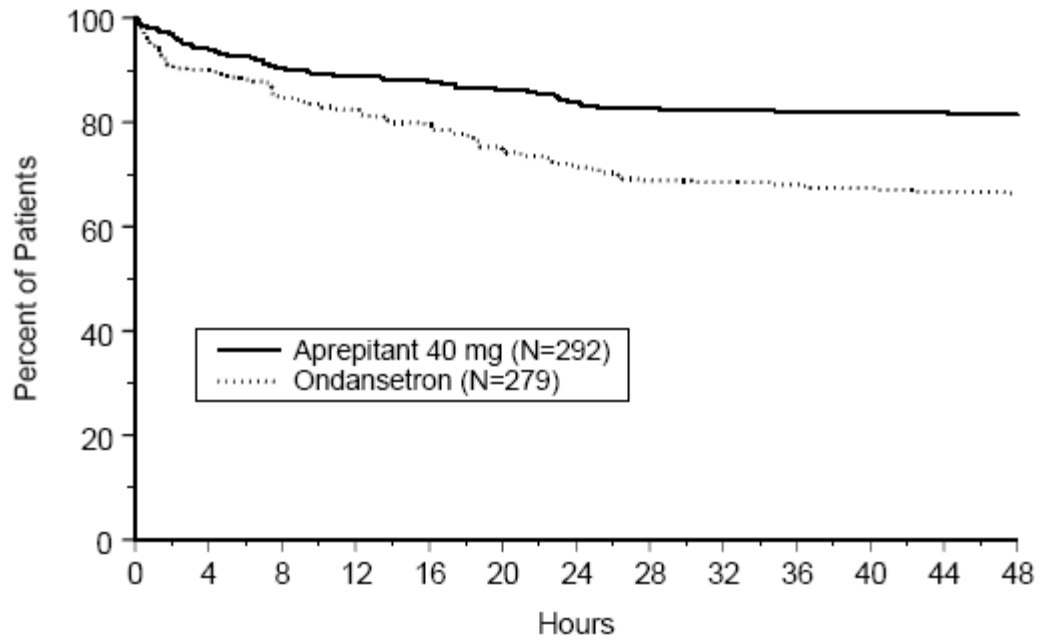
PONV Study 1 Results (Summarized in Table 6):

- For the primary endpoint of no emesis in the first 24 hours following then end of surgery, aprepitant 40 mg was found to be statistically superior to Ondansetron 4 mg IV based on Odds Ratio analyses.
- For the primary endpoint of Complete Response, aprepitant 40 mg was found to be non-inferior and comparable to Ondansetron 4 mg IV.
 - A superiority test was then conducted and showed that aprepitant 40 mg was not superior to Ondansetron 4 mg IV for the primary endpoint of Complete Response.
- For the secondary endpoint of No emesis in the first 48 hours following surgery, aprepitant 40 mg was found to be superior to Ondansetron 4 mg IV
- The time to first use of rescue medication in the first 24 hours following the end of surgery was not found to be different between the aprepitant 40 mg group and the Ondansetron 4 mg IV group (Not shown in Table 4).
- The time to first emesis in the first 48 hours following surgery results are shown in the Kaplan Meier Curve in Figure 3.
 - According to the researchers, this figure shows that aprepitant delays the onset of vomiting compared to Ondansetron.

Table 6
PONV Study 1 Multinational
Response Rates for Select Efficacy Endpoints
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant Vs Ondansetron	
		Δ	Analysis
Primary Endpoints			
No Vomiting 0 to 24 hours (Superiority) (no emetic episodes)			
Aprepitant 40 mg	246/293 (84.0)	12.6%	P<0.001*
Ondansetron 4 mg	200/280 (71.4)		
Complete Response (Non-inferiority: if LB >0.65) (no emesis and no rescue therapy, 0 to 24 hours)			
Aprepitant 40 mg	187/293 (63.8)	8.8%	LB=1.02
Ondansetron 4 mg	154/280 (55.0)		
Secondary Endpoint			
No Vomiting 0 to 48 hours (Superiority) (no emetic episodes)			
Aprepitant 40 mg	238/292 (81.5)	15.2%	P<0.001*
Ondansetron 4 mg	185/279 (66.3)		
n/m = Number of responders/number of patients in analysis. Δ Difference (%): Aprepitant 40 mg minus Ondansetron 4 mg. *P-value of two-sided test <0.05. LB = lower bound of 1-sides 97.5% confidence interval for the odds ratio.			

Figure 3
Percent of Patients Who Remain Emesis Free
During the 48 Hours Following End of Surgery



Efficacy measures in PONV Study 2:

- Complete response (no emesis or use of rescue therapy for established nausea or vomiting) in the first 24 hours following end of surgery (Primary Endpoint)
- No emesis (no emetic episodes regardless of rescue therapy) in the first 24 hours following end of surgery (Secondary Endpoint)
- No use of rescue therapy in the first 24 hours following the end of surgery (Secondary Endpoint)
- No emesis (no emetic episodes regardless of rescue therapy) in the first 48 hours following end of surgery (Secondary Endpoint)

PONV Study 2 Results (Summarized in Table 7):

- Aprepitant is not superior to ondansetron in the prevention of PONV regarding complete response as the number of patients with complete response was not significantly different between the groups.
- There was a difference between the aprepitant group and the ondansetron group for the secondary endpoints of no vomiting at 24 and 48 hours, however this difference was not found to be statistically significant after pre-specified multiplicity adjustment.
- The secondary endpoint of No use of rescue therapy in the first 24 hours following the end of surgery did not show a statistically significant difference.

Table 7
PONV Study 2 United States
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant Vs Ondansetron
		Δ
Primary Endpoint		
Complete Response (no emesis and no rescue therapy, 0 to 24 hours)		
Aprepitant 40 mg	111/248 (44.8)	2.5%
Ondansetron 4 mg	104/246 (42.3)	
Secondary Endpoints		
No Vomiting (no emetic episodes, 0 to 24 hours)		
Aprepitant 40 mg	223/248 (89.9)	16.3%
Ondansetron 4 mg	181/246 (73.6)	
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)		
Aprepitant 40 mg	112/248 (45.2)	-0.7%
Ondansetron 4 mg	113/246 (45.9)	
No Vomiting 0 to 48 hours (Superiority) (no emetic episodes, 0 to 48 hours)		
Aprepitant 40 mg	209/247 (84.6)	17.7%
Ondansetron 4 mg	164/245 (66.9)	
n/m = Number of responders/number of patients in analysis. Δ Difference (%): Aprepitant 40 mg minus Ondansetron 4 mg. In Study 2, the researchers were unable to show a statistically significant difference between aprepitant and Ondansetron for the endpoints studied.		