

Pharmacy & Therapeutic Committee  
Emend (aprepitant)  
7/2003

**Recommendations: P&T/MEC approved MRMC/RCH/ SMH**

- Oral Aprepitant (Emend™) is recommended for addition to the formulary.
- Oral Aprepitant, in combination with a 5HT3 antagonist and dexamethasone, is FDA approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (including high dose cisplatin).
- The FDA recommended dosage of aprepitant, 1 hour before chemotherapy, is 125mg orally on day 1 and 80mg orally on days 2 - 3, along with a 5HT3 receptor antagonist on day 1, and dexamethasone on days 1-4.
- Granisetron 2 mg PO and dexamethasone PO are recommended to be given in combination Aprepitant as efficacy is unchanged and cost is reduced by using the oral route. *The American Society of Clinical Oncology recommends the oral route.* Orders will be entered for the oral route unless the patient is unable to use oral route.

Findings:

- Aprepitant, in combination with other antiemetics agents, is FDA approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (including high dose cisplatin).
- Chronic continuous use of aprepitant is not recommended.
- Aprepitant is a highly selective antagonist of human substance P/neurokinin 1 (NK<sub>1</sub>) receptors.
- Aprepitant crosses the blood brain barrier and occupies the NK1 receptors.
- The NK1 receptors mediate the biological activities of Substance P. Substance P and the receptors are located in the brainstem dorsal vagal complex and in the GI tract. Chemotherapeutic agents activate the Chemoreceptor trigger zone (CTZ) by releasing various neurotransmitters (including Substance P) both peripherally and centrally to induce chemo nausea and vomiting.
- Aprepitant has little or no affinity for serotonin (5-HT<sub>3</sub>), dopamine, and corticosteroid receptors.
- Aprepitant is eliminated primarily by metabolism and is not renally excreted. Therefore, no dosage adjustment is necessary in the elderly, patients with mild to moderate *hepatic insufficiency (Child-Pugh score of 5-9)*, patients with *renal insufficiency (CrCl < 30mL/min)*, and patients with ESRD undergoing hemodialysis. Studies have not be conducted in patients with Child-Pugh scores > 9.
- Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. It should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride.
- Aprepitant is an inducer of CYP2C9, increases the metabolism of warfarin and tolbutamide.
- Interactions with granisetron or ondansetron have not been demonstrated.
- Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical studies aprepitant was commonly administered with etoposide, vinorelbine, or paclitaxel. The doses of these agents where not altered to account for potential drug interactions. Small number of patients in clinical studies received docetaxel, vinblastine, vincristine or ifosfamide.
- Dosage and administration: 125 mg PO 1 hours before chemotherapy on day 1, 80 mg PO 1 hour before chemotherapy on days 2 and 3.

Aprepitant Package Insert (Study One / Two)		
	Aprepitant N=260	Standard Therapy N=261
Complete Response *		
Overall	73% / 63%	52% / 43 %
Acute Phase	89% / 83%	78% / 68%
Delayed Phase	75% / 68%	56% / 47%
Complete Protection <sup>+</sup>		
Overall	63% / 56%	49% / 41%
Acute Phase	85% / 80%	75% / 65%
Delayed Phase	66% / 61%	52% / 44%

\*Complete Response: No emetic episodes & no use of rescue therapy

<sup>+</sup>Complete Protection: No emetic episodes, no use of rescue therapy, and a maximum nausea visual analog scale < 25 mm on a 0-100 scale.

Pharmacokinetics	
Bioavailability	65%
Time to Peak	4 hours
Food Effect	Negligible
AUC (mcg/hr/ml) day 1/day3 3	19.6 / 21.2
Cmax Day 1/ day 3	1.6 mcg/ml, 1.4 mcg/ml
Protein Binding	95%
Volume of Distribution	70 liters
Plasma Clearance	3.72-5.4 liter/hour
Metabolic Pathways	Major CYP3A4 , Minor CYP1A2, CYP2C19
Renal Elimination	Negligible
Half-life	9-13 hours

- Emend is a moderate CYP3A4 substrate/moderate inhibitor/inducer and also an inducer of CYP2C9 therefore, certain precautions apply.

Drug Interactions Listed In The Package Insert		
Interaction Drug	Drugs that Affect Aprepitant	Action
Dexamethasone	Dexamethasone AUC increases 2.2 fold	Cut dose of dexamethasone by 50%
Methylprednisolone	Methylprednisolone AUC increases 2.5 fold on day 3	Decrease IV dose of methylprednisolone by 25% and oral dose 50%
Midazolam (alprazolam, triazolam)	Midazolam AUC increases 3 fold.	Decrease dose of midazolam or use alternative agent
Oral contraceptives	AUC decreases 43%	Use alternative contraceptive method
Tolbutamide	Tolbutamide AUC decreases 23 %	Higher dose of tolbutamide may be needed
Warfarin	Lower plasma warfarin concentrations, 14% decrease in INR	Higher dose of warfarin may be needed. Close monitoring for 2 weeks.
<b>Drugs that Affect Aprepitant</b>		
Ketoconazole, Itraconazole, Nefazodone, Troleandomycin, Clarithromycin, Ritonavir, Nelfinavir, or Diltiazem	Increased plasma concentrations of aprepitant $\geq$ 2 fold	Approach with caution
Rifampin, Carbamazepine, or Phenytoin	Decreased plasma concentrations of aprepitant.	Rifampin will negate aprepitant's effect.
Paroxetine	20% decrease in AUC of aprepitant and paroxetine.	

<b>DRUG INTERACTIONS WITH APREPITANT</b>			
	<b>Drugs</b>	<b>Interactions</b>	<b>Action</b>
<b>CYP3A4 Inhibitors</b>	Ketoconazole, Itraconazole, Nefazodone, Troleandomycin, Clarithromycin, Ritonavir, Nelfinavir, or Diltiazem	Increased plasma Concentrations of aprepitant $\geq 2$ fold	Approach with caution
<b>CYP3A4 Inducers</b>	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
<b>CYP3A4 Substrate (Aprepitant Metabolism)</b>	<b>Dexamethasone</b>	Increases AUC of Dexamethasone	<b>Decrease oral Dexamethasone dose by 50% when co-administered w/Aprepitant</b>
	Pimozide, Terfenadine, Astemizole, or Cisapride	Elevated plasma Concentrations	<b>Do not use</b> Aprepitant concurrently With these medications
	Etoposide, Vinorelbine, or Paclitaxel	Elevated plasma Concentrations	It was used in a small # of pts in a Study, however caution and careful monitoring are advised
	Midazolam and other Benzodiazepines metabolized Via CYP3A4 such as Alprazolam and Triazolam	Increased plasma Concentrations	Use alternative agent.
	<b>Methylprednisolone</b>	Increased AUC of Methylprednisolone	<b>Reduce the IV dosage by 25% and the oral dosage by 50% when administered with Aprepitant</b>
	Oral Contraceptives	Decreased efficacy	Make sure to use alternative or backup Methods
<b>CYP2C9 Substrate</b>	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
	Tolbutamide, Phenytoin	Decreased plasma Concentrations	Monitor plasma levels, blood sugar or symptom profile

See the PI for more complete details.

<b>COST SUMMARY</b>	
IV Zofran 32mg x 1 day	\$134.85
PO Emend (125mg x 1; 80mg x 2) for 3 days	\$237.65
PO Decadron (12mg x 1; 8mg days 2-4)	\$1.00
<b>Total Cost</b>	<b>\$373.50</b>

IV Kytril 1mg x 1 day	\$82.47
PO Emend (125mg x 1; 80mg x 2) for 3 days	\$237.65
PO Decadron (12mg x 1; 8mg days 2-4)	\$1.00
<b>Total Cost</b>	<b>\$321.12</b>

PO Kytril 2mg x 1 day	\$47.04
PO Emend (125mg x 1; 80mg x 2) for 3 days	\$237.65
PO Decadron (12mg x 1; 8mg days 2-4)	\$1.00
<b>Total Cost</b>	<b>\$285.69</b>