



# Pharmacy

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# Update

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## Aprepitant (Emend®) – Review of a New Antiemetic Agent and Guidelines for Use at the NIH Clinical Center

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Aprepitant is a new antiemetic agent recently approved by the Food and Drug Administration for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic cancer chemotherapy. It is the first FDA-approved agent within a new pharmacologic class of drugs referred to as neurokinin-1 (NK<sub>1</sub>) receptor antagonists. On May 22, 2003, the NIH Clinical Center (NIH CC) Pharmacy and Therapeutics Committee approved adding aprepitant to the NIH CC formulary. However, due to risks associated with aprepitant use with respect to potential drug interactions, for causing or exacerbating adverse effects, and its drug cost, it was approved with specific recommendations and guidelines for use. These recommendations and guidelines were developed by the NIH CC Antiemetic Task Force and appear in the boxed information that accompanies this monograph.

### Aprepitant – Recommendations and Guidelines for Use

(NIH CC Antiemetic Task Force, May 2003)

Aprepitant has been shown to significantly improve the prevention of both acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic (cisplatin-based) chemotherapy when combined with a 5-HT<sub>3</sub> antagonist and a high-potency glucocorticoid. However, there are several important caveats attendant to its rational utilization:

- 1) aprepitant has not been shown to mitigate ongoing emetic symptoms.
- 2) it has not been adequately tested in person <18 years of age and presently is indicated only in adult patients.
- 3) its use is complicated by a potential for pharmacokinetic interactions with other drugs and foods that affect and are affected by particular cytochrome P450 isoenzymes (CYP2C9, CYP3A4, and perhaps CYP2D6).
- 4) it has not been tested for continuous use for durations greater than five days in patients receiving emetogenic chemotherapy, and
- 5) it is prohibitively expensive.

For these reasons, aprepitant should be prescribed for CINV prophylaxis in adult patients only after carefully considering whether it is needed for emetic control during the acute, delayed, or both periods; the risks associated with its potential for interacting with concomitantly administered medications; its potential for causing or exacerbating adverse effects; and the financial costs associated with its use.

### General Recommendations

#### (NIH CC Antiemetic Task Force, May 2003)

- ❖ Aprepitant should only be prescribed for the prophylaxis of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy (> 30% incidence of emesis) in adult patients (> 18 years of age).
  - Aprepitant should be used in combination with, and not as a replacement for, a prophylactic CINV regimen that includes a 5-HT<sub>3</sub> antagonist (e.g., ondansetron) for prevention of acute CINV.
  - Aprepitant should not be utilized to treat established nausea and vomiting, regardless of its etiology.
  - Aprepitant should not be prescribed on a “PRN” basis.
- ❖ When utilized for CINV prophylaxis with a research protocol chemotherapy regimen, aprepitant should only be prescribed with the knowledge and approval of a medically-responsible study investigator. It is a prescriber’s responsibility to inform a medically-responsible investigator about aprepitant use for each patient.
  - The above recommendation is based on the known and suspected drug-drug interactions and potential toxicities associated with aprepitant which could lead to adverse patient outcomes and compromise patient safety and protocol integrity.

### Guidelines for Prescribing Aprepitant

#### (NIH CC Antiemetic Task Force, May 2003)

- ❖ Chemotherapy-Induced Nausea & Vomiting (CINV) Prophylaxis – High Emetic Risk (> 30% risk of emesis)
  - Aprepitant 125 mg PO x 1 dose given 1 hour prior to chemotherapy may be combined with a 5-HT<sub>3</sub> antagonist (e.g., ondansetron) and a high-potency glucocorticoid (e.g., dexamethasone).
  - *Grade of recommendation: A*
    - If a chemotherapy regimen is a multiple-day regimen, a 125-mg dose of aprepitant should be given only on the first day chemotherapy is given. On subsequent days, aprepitant 80 mg should be given once daily before chemotherapy with a total duration of aprepitant to not exceed five days.  
*Note:* Aprepitant has not been evaluated with multiple-day chemotherapy regimens.
  - *Grade of recommendation: D*
    - If aprepitant is combined with a glucocorticoid, orally-administered glucocorticoid doses should be reduced by 50%, and 25% for glucocorticoids given parenterally.  
*Note:* Steroids are not permitted in some research protocols.

#### Example regimens (Day 1 of chemotherapy):

Ondansetron 24 mg PO x 1 given 30 min prior to chemotherapy + Dexamethasone 8-12 mg PO x 1 given 30 min prior to chemotherapy + Aprepitant 125 mg PO x 1 given 60 min prior to chemotherapy  
**OR**

### Pharmacology

Aprepitant is a selective, high-affinity, competitive antagonist at human NK<sub>1</sub> receptors that blocks the physiologic effects of substance P, the natural ligand, which has been shown to induce CINV. It has little or no affinity for other neuro-receptors that are targeted by existing pharmacologic agents for chemotherapy-induced nausea and vomiting.<sup>1</sup>

In animal models, aprepitant inhibits emesis induced by emetogenic chemotherapy, such as cisplatin, via central actions.<sup>1</sup> Pharmacodynamic studies in animals and humans have demonstrated that aprepitant, as a single agent, decreases the incidence of vomiting after emetogenic chemotherapy, augments the antiemetic activity of ondansetron and dexamethasone, and inhibits both the acute and delayed emetic phases associated with cisplatin.<sup>3</sup>

Clinical pharmacology studies have demonstrated a correlation between plasma concentrations of aprepitant and its binding to brain NK<sub>1</sub> receptors. In an analysis of antiemetic responses among patients who received *standard prophylaxis* with ondansetron and dexamethasone with or without aprepitant at one of two dose levels, the administered dose of aprepitant was a statistically significant predictor of complete response.<sup>3</sup> Maximum efficacy was achieved with a loading dose of aprepitant 125 mg given before chemotherapy, followed by aprepitant 80 mg/day on subsequent days and there was no apparent benefit at the highest dose regimen of 375 mg (loading dose), followed by 250 mg/day (subsequent days).<sup>3</sup> Trough concentrations with a 125-mg (day 1) + 80-mg (subsequent days) regimen are predicted to provide >95% NK<sub>1</sub> receptor blockade, which correlates with maximal antiemetic response.<sup>1</sup>

### Pharmacokinetics

#### Absorption

Aprepitant’s mean absolute oral bioavailability is approximately 60–65%.<sup>1</sup> Mean peak aprepitant concentrations in plasma occur at approximately four hours after oral ingestion. Oral administration with a standard breakfast has no clinically meaningful effect on aprepitant bioavailability. Aprepitant’s pharmacokinetics are slightly nonlinear with approximately 25% higher area under the plasma concentration vs. time curve (AUC<sub>0-∞</sub>) after 125 mg than an 80-mg dose.<sup>1</sup>

#### Distribution

Aprepitant is >95% bound to plasma proteins in healthy subjects; its mean apparent volume of distribution is 66 L in humans.<sup>1</sup> Aprepitant crosses the placenta in rats and rabbits and crosses the blood-brain barrier in humans.

#### Metabolism

Aprepitant undergoes hepatic metabolism that is principally catalyzed by the cytochrome P450 (CYP) CYP3A4 isoform, with minor contributions from the CYP1A2 and polymorphic CYP2C19 isoforms. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours after a single oral 300-mg dose of <sup>14</sup>C-labeled aprepitant, which indicates a substantial

presence of metabolites in plasma. Seven weakly active aprepitant metabolites have been identified in human plasma.<sup>1</sup>

### Elimination

Following intravenous administration of a single 100-mg dose of <sup>14</sup>C-L-758298 (aprepitant prodrug) to healthy subjects, 58% of the radioactivity was recovered in urine and 45% in feces. The prodrug was shown to be completely and rapidly converted to aprepitant, *in vivo*. No unchanged aprepitant was detected in urine. Overall, it appears that aprepitant undergoes extensive metabolism and is primarily eliminated via excretion of metabolites. Following intravenous administration, aprepitant's apparent plasma clearance varies from approximately 62–90 mL/min (mean, 84 mL/min), and its apparent terminal half-life ( $t_{1/2}$ ) ranges from 9–13 hours.<sup>1</sup>

### Selected Clinical Studies

The severity, time course, and ways in which chemotherapy-induced emesis manifest depend on the antineoplastic agents used, their dosages and administration schedule. New antiemetic agents and drug combination strategies often are tested against chemotherapy regimens containing cisplatin because almost all patients who receive cisplatin at dosages  $\geq 50$  mg/m<sup>2</sup> without antiemetic prophylaxis will experience severe acute emesis<sup>4</sup> and 57–89% of patients will experience delayed emesis.<sup>5–7</sup> Although serotonin receptor antagonists prevent acute emesis in 45–60% of patients and better acute control is achieved by the addition of dexamethasone<sup>8–12</sup>, serotonin antagonists have not proven to be very effective against delayed-phase symptoms.<sup>13,14</sup> The current approach to preventing delayed emesis that is endorsed by expert groups and recommended in consensus guidelines is a combination of dexamethasone with either metoclopramide or a serotonin antagonist,<sup>15–18</sup> which has been shown to prevent delayed emesis in 52–69% of patients.<sup>7,19</sup> The NK<sub>1</sub> receptor antagonists provide a new pharmacologic approach to CINV prophylaxis with the potential to improve efficacy for both the acute and delayed phases of CINV.

In early clinical trials, aprepitant or a precursor drug that was systemically metabolized to aprepitant were compared with a serotonin receptor subtype-3 (5-HT<sub>3</sub>) antagonist (e.g., ondansetron)-based regimen. Although active, aprepitant was shown to be inferior than a 5-HT<sub>3</sub> antagonist for acute phase CINV, but showed superior efficacy against delayed phase symptoms.<sup>23,24</sup> When aprepitant was added to standard antiemetic prophylaxis that included a 5-HT<sub>3</sub> antagonist and dexamethasone, aprepitant improved efficacy in both the acute and delayed phases.<sup>20,24</sup> Subsequently, phase II and phase III trials were designed which further evaluated aprepitant's role in a combination regimen that included a 5-HT<sub>3</sub> antagonist and a high potency steroid such as dexamethasone.

### Phase II dose evaluation

Chawla et al, reported a multicenter, randomized, double-blind, placebo-controlled study in which they compared two aprepitant-based antiemetic regimens for efficacy and toxicity during patients' initial treatment with

Ondansetron 0.15 mg/kg IV x 1 given 30 min prior to chemotherapy + Dexamethasone 8-12 mg IV x 1 given 30 min prior to chemotherapy + Aprepitant 125 mg PO x 1 given 60 min prior to chemotherapy

### ❖ Delayed CINV Prophylaxis (cisplatin and non-cisplatin regimens)

- Aprepitant 80 mg PO daily for two consecutive days can be given in combination with dexamethasone, or as a single agent, starting 16-24 hours (e.g., the morning after) after the last dose of highly-emetogenic chemotherapy for delayed CINV prophylaxis. (See NIH CC Antiemetic Guidelines for examples of non-cisplatin regimens associated with delayed CINV [<http://internal.cc.nih.gov/formulary>].) When given on more than one day, aprepitant is given on consecutive days and its total duration of use should not exceed five days.
- *Grade of recommendation in cisplatin-based regimens: A*
- *Grade of recommendation in non-cisplatin regimens: D*
  - In clinical studies that demonstrated reduced delayed nausea and vomiting symptoms, aprepitant was always given on the day of chemotherapy, followed by additional days after chemotherapy. There is no experience giving aprepitant solely after chemotherapy. It is therefore recommended that if aprepitant is used for CINV prophylaxis that it be started on the first day that chemotherapy is given.
  - When combined with aprepitant, orally-administered dexamethasone doses should be reduced by 50%, parenteral doses by 25%, and doses generally should not exceed 8mg/day by either administration route.

### Example regimens:

Aprepitant 80 mg PO daily x 2 doses starting 16-24 hrs after chemotherapy + Dexamethasone 8 mg PO daily x 3 doses starting 16-24 hrs after chemotherapy  
**OR** (if dexamethasone is not permitted)  
Aprepitant 80 mg PO daily x 2 doses starting 16-24 hrs after chemotherapy

*Note:* The aprepitant regimens and dosing recommendations for CINV prophylaxis have been graded by the NIH Clinical Center Antiemetic Task Force according to the strength of scientific evidence that support their use. The dosing regimens are graded A, B, C, or D based on the following criteria:

- A. Strong research-based evidence (multiple large, randomized, controlled trials or meta-analyses of such trials),
- B. Moderate research-based evidence (evidence is obtained from at least one well-designed, randomized, clinical trial),
- C. Limited research-based evidence (formal clinical trials were of less rigorous design than the definitions described for grades A or B), and
- D. Panel interpretation of information that did not meet inclusion criteria as research-based evidence as described for grades A-C.

cisplatin  $\geq 70$  mg/m<sup>2</sup>.<sup>3</sup> All patients received standard antiemetic prophylaxis with ondansetron and dexamethasone before chemotherapy plus dexamethasone on days 2–5, and were randomly assigned to receive either aprepitant or placebo (see study schema in Table 1). The study's design was altered after pharmacokinetic data became available from a study in normal volunteers which revealed that an "aprepitant 375/250" regimen resulted in greater aprepitant plasma concentrations than had been anticipated, probably greater than were required to occupy >90% of central nervous system NK<sub>1</sub> receptors. In addition, data suggested an interaction between aprepitant at that dose and schedule and dexamethasone that resulted in delayed dexamethasone elimination. Subsequently, the trial was changed and a new randomization schedule was generated. In the final analyses, all patients who received aprepitant were included in an assessment of tolerability; however, efficacy analysis included only patients who received aprepitant after the high-dose regimen was adjusted.

**Table 1. Study Design (Chawla, et al.<sup>3</sup>)**

Study Groups	Day 1	Days 2–5
<b>aprepitant 375/250</b>	ondansetron 32 mg IV & dexamethasone 20 mg PO, 30 min before CTx + aprepitant 375 mg PO, 60 min before CTx	dexamethasone 8 mg/d x4 d PO + aprepitant 250 mg/d x4 d PO
	<i>regimen was changed to:</i>	<i>regimen was changed to:</i>
<b>aprepitant 40/25</b>	ondansetron 32 mg IV and dexamethasone 20 mg PO, 30 min before CTx + aprepitant 40 mg PO, 60 min before CTx	dexamethasone 8 mg/d x4 d PO + aprepitant 25 mg/d x4 d PO
<b>aprepitant 125/80</b>	ondansetron 32 mg IV & dexamethasone 20 mg PO, 30 min before CTx + aprepitant 125 mg PO, 60 min before CTx	dexamethasone 8 mg/d x4 d PO + aprepitant 80 mg/d x4 d PO
<b>standard prophylaxis</b>	ondansetron 32 mg IV & dexamethasone 20 mg PO, 30 min before CTx + placebo, 60 min before CTx	dexamethasone 8 mg/d x4 d PO + placebo

The responses from this trial are summarized in Table 2. Overall, complete responses (no emesis, no rescue therapy) among patients who received either aprepitant regimen was significantly greater during both the acute (day 1) and delayed phases (days 2–5) than in patients who received only standard prophylaxis.<sup>3</sup> In contrast, differences between standard prophylaxis and the aprepitant 40/25 regimen were less consistently observed. In spite of being

based on a small number of patients, efficacy findings for the aprepitant 375/250 regimen for all three intervals (overall [d 1–5], acute, and delayed phases) were very similar to those observed for aprepitant 125/80, which suggests that aprepitant doses greater than the aprepitant 125/80 regimen would not improve its antiemetic benefit.<sup>3</sup> The analyses also revealed that aprepitant 125/80 was superior to standard prophylaxis with respect to no emesis and complete protection from acute phase symptoms (i.e., no emesis, no significant nausea, no rescue medications).

**Table 2. Clinical Response Data (Chawla, et al.<sup>3</sup>)**

Complete Responses	Aprepitant 125/80*	Aprepitant 40/25*	Standard Prophylaxis
d 1	83.2%†	75.6%	71.4%
d 2–5	72.7%‡	63.9%§	45.2%
d 1–5	71% (n=131)	58.8% (n=119)†	43.7% (n=126)

\* aprepitant regimens included standard prophylaxis

† P <0.05 vs. standard prophylaxis

‡ P <0.001 vs. standard prophylaxis

§ P <0.002 vs. standard prophylaxis

|| P <0.01 vs. standard prophylaxis

The investigators concluded that aprepitant reduced chemotherapy-induced nausea and vomiting when added to a standard regimen of intravenous ondansetron and oral dexamethasone and was generally well tolerated, although increases in infection were noted that were assumed to be due to increased dexamethasone concentrations and delayed clearance as a result of its pharmacokinetic interaction with aprepitant. The aprepitant 125/80-mg regimen had the most favorable benefit:risk profile.

#### Phase III trials

Merck & Co, Inc., submitted two phase III trials in support of the proposed indication for preventing acute and delayed nausea and vomiting associated with initial and repeated courses of cisplatin (>50 mg/m<sup>2</sup> in all patients;  $\geq 70$  mg/m<sup>2</sup> in ~80% of patients) either alone or with concomitant chemotherapy (studies #052 & #054).<sup>1</sup> The results of these trials have not yet been published in a peer-reviewed medical journal. The two trials were identical in design, except Study 052 was amended to allow for the inclusion of four adolescent patients. Both studies were multicenter, randomized, parallel, double-blind, controlled trials. The total enrollment for both trials combined was 1105 patients. The majority of patients (95%) who received aprepitant received one or more chemotherapeutic agents in addition to cisplatin, most commonly: etoposide, fluorouracil, gemcitabine, vinorelbine, paclitaxel, cyclophosphamide, doxorubicin, and docetaxel.<sup>2</sup>

The treatment regimens for studies 052 and 054 are identified in Table 3.

**Table 3. Experimental Treatment for Study 052 and Study 054<sup>1</sup>**

Study Groups	Day 1	Days 2–4
<b>aprepitant group</b>	aprepitant 125 mg PO + dexamethasone 12 mg PO + ondansetron 32 mg IV	aprepitant 80 mg/d PO (days 2 & 3 only) + dexamethasone 8 mg/d PO (morning, days 2–4) + dexamethasone placebo PO (evening, days 2–4)
<b>standard prophylaxis group</b>	aprepitant placebo PO + dexamethasone 20 mg PO + ondansetron 32 mg IV	aprepitant placebo PO (days 2 & 3 only) + dexamethasone 8 mg/d PO (morning, days 2–4) + dexamethasone 8 mg/d PO (evening, days 2–4)

In adolescent patients (12 and <18 years of age and = 40 kg body weight), ondansetron 0.15 mg/kg IV was administered 30 min before cisplatin, and subsequent doses were given at 4 h and 8 h afterward.

Efficacy was evaluated for the acute phase (0–24 h after cisplatin), the delayed phase (25–120 h after cisplatin), and overall (0–120 h after cisplatin) during patients' first cycle of chemotherapy. The primary study endpoint was the complete response rate, which was defined as no emetic episodes and no use of rescue therapy. Secondary endpoints included the incidence of complete protection (no emesis, no rescue therapy, and minimal nausea), the incidence of no emesis, no nausea, and no significant nausea. The complete response rates are summarized in Table 4.

The results clearly demonstrate that aprepitant improved upon the efficacy of a standard CINV prophylaxis regimen consisting of a 5-HT<sub>3</sub> antagonist (ondansetron) and dexamethasone during both the acute and delayed phases, particularly for the primary study endpoint. The clinical benefit of aprepitant on the nausea endpoints (no nausea or no significant nausea) was less clear, but may have been affected by the use of antiemetic "rescue" therapy

**Table 4. Summary Efficacy Results of Study 052 and 054<sup>1</sup>**

	Aprepitant Regimen	Standard Prophylaxis
<b>Complete Responses</b> (no emetic episodes, no rescue medications)		
<b>Study 052</b>		
Overall (d 1–5)*	72.7%†	52.3%
Acute phase (d 1)	89.2%†	78.1%
Delayed phase (d 2–5)	75.4%†	55.8%
<b>Study 054</b>		
Overall*	62.7%†	43.3%
Acute phase	82.8%†	68.4%
Delayed phase	67.7%†	46.8%

\* primary endpoint

† p<0.01 when compared with Standard Prophylaxis

because a greater proportion of patients who received standard prophylaxis required antiemetic rescue.<sup>1</sup> The FDA, during its evaluation of the phase III studies, noted that Merck & Co., Inc., studied safety and efficacy only with highly emetogenic doses of cisplatin ± other concomitant chemotherapy. The safety and efficacy of an aprepitant regimen with non-cisplatin highly emetogenic chemotherapy has not been evaluated.<sup>1</sup>

### Adverse Effects

Clinical adverse events that were reported in phase II trials in >10% of patients studied included constipation,<sup>3,24</sup> diarrhea,<sup>3,24</sup> abdominal pain,<sup>24,25</sup> dizziness,<sup>24,25</sup> headache,<sup>3,24,25</sup> hiccups,<sup>3,24,25</sup> asthenia,<sup>3,24,25</sup> fatigue,<sup>3</sup> and anorexia,<sup>3,24</sup> and neutropenia;<sup>3</sup> however, there were no significant differences in the incidence of these adverse events among comparator groups except for a higher incidence of diarrhea in patients who did not receive a 5-HT<sub>3</sub> receptor antagonist.<sup>24,25</sup>

It should be noted that cisplatin has been shown to cause diarrhea in up to 60% of patients when it is administered without antiemetics,<sup>26</sup> an effect which 5-HT<sub>3</sub> antiemetics have been shown to mitigate.<sup>27,28</sup> Thus a greater incidence of diarrhea observed in patients who received aprepitant without a 5-HT<sub>3</sub> receptor antagonist may reflect a loss of a 'protective effect' provided by 5-HT<sub>3</sub> antagonists rather than a pharmacodynamic effect attributable to aprepitant.

In a phase II randomized clinical trial, no significant differences were observed among the treatment groups with respect to laboratory indices of safety (on the basis of an analysis of the proportion of patients in each group with NCI toxicity grades 3 or 4 for laboratory results).<sup>24</sup>

Of the 580 patients who were eligible for safety assessment in the phase II trial conducted by Chawla et al., 428 (73.7%) reported clinical adverse events after treatment.<sup>3</sup> Serious clinical adverse events were observed more frequently in the aprepitant groups in comparison with patients who received standard prophylaxis. In particular, patients who received aprepitant 125/80 had the greatest rates of adverse events, drug-related adverse events, and discontinuations due to serious adverse events, but the relative risks for these categories did not achieve a statistically significant difference whether patients received aprepitant with or without standard prophylaxis (ondansetron + dexamethasone).<sup>3</sup> There was a difference noted in the relative frequency of infection-related serious adverse events (documented infections or reports of febrile neutropenia) observed between the aprepitant 125/80-mg (28 patients; 13%) and standard prophylaxis (nine patients; 4.2%) groups. This increased rate of infection-related serious adverse events did not appear to be related to myelosuppression as the difference in risk for febrile neutropenia did not reach significance based on a pre-specified analysis.<sup>3</sup> The investigators postulated that the increased risk of infectious-related complications was related to the pharmacokinetic drug interaction between aprepitant and dexamethasone that led to higher plasma

concentrations of dexamethasone. Based on this experience, the dexamethasone regimens were modified in phase III trials in an attempt to reduce dexamethasone exposure so that it was comparable to standard prophylaxis.<sup>3</sup>

In two phase III clinical trials, 544 patients received aprepitant prophylaxis with their first treatment cycle of highly emetogenic chemotherapy, and 413 of these patients continued into the multiple-cycle extension for up to six cycles of chemotherapy. Most adverse experiences reported in the phase III studies were described as mild to moderate in intensity. Clinical adverse experiences were reported in approximately 69% of patients who received an aprepitant regimen in comparison with approximately 68% of patients who received standard antiemetic prophylaxis.<sup>2</sup> The incidences of adverse events were comparable between the comparator groups. The adverse experience profiles observed during up to six cycles of chemotherapy were generally similar to what had been observed during patients' first cycle.<sup>2</sup>

### **Drug Interactions**

Aprepitant is a substrate, a moderate inhibitor, and an inducer of the microsomal cytochrome P450 CYP3A4 isoform; i.e., it may affect, and conversely, its pharmacokinetics may be affected by other drugs that are metabolized by CYP3A4.<sup>1</sup> Drugs that inhibit CYP3A4 activity may result in increased aprepitant concentrations in plasma. Therefore, concomitant administration of aprepitant with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, troleandomycin, ritonavir, voriconazole) should be approached with caution.<sup>2</sup> Coadministration with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in decreased aprepitant plasma concentrations with a corresponding loss of antiemetic activity.<sup>2</sup> CYP3A4 is expressed on gastrointestinal epithelial cells as well as intrahepatically. Consequently, aprepitant's effect on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than on intravenously-administered CYP3A4 substrates.

### **Potential Drug Interactions**

Chemotherapy agents that are known to be metabolized to some degree by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine.<sup>2</sup> In clinical studies, aprepitant was administered commonly with CYP3A4 substrates, including: etoposide, vinorelbine, or paclitaxel. Although the number of patients who received aprepitant concomitantly with docetaxel, vinblastine, vincristine, or ifosfamide was too small to conclude whether aprepitant dose and schedule modifications are necessary, caution and careful monitoring are advised in patients who receive these and other drugs with a low therapeutic index that are metabolized primarily by CYP3A4.<sup>2</sup>

Prior to receiving FDA approval for marketing, the FDA Medical Officer's summary expressed, "concerns regarding the potential for aprepitant to alter the pharmacokinetics of therapeutic agents via CYP3A4 interaction."<sup>1</sup> There are no pharmacokinetic data available regarding the drug-drug interaction of the aprepitant regimen on chemotherapeutic agents metabolized by CYP3A4." The Medical Officer noted that, "Two hundred sixty-six patients in the aprepitant group and 251 patients in the standard therapy group received, in addition to cisplatin, a concomitant chemotherapy metabolized by CYP3A4 [most commonly: cyclophosphamide, etoposide, fluorouracil, gemcitabine, paclitaxel, and vinorelbine tartrate]. Overall, the incidence of serious adverse experiences in this subpopulation was slightly higher in the aprepitant group than the standard therapy group (15.0% vs. 13.5%, respectively).<sup>1</sup> There were more infection-related serious adverse events reported in the aprepitant group. In the aprepitant group, septic shock was reported in three patients, sepsis in one patient, and upper respiratory infection in one patient. In the corresponding standard therapy group there were no reports of these serious adverse events.<sup>1</sup> A higher incidence of hematologic serious adverse events was also seen in this subpopulation. Neutropenia was reported as a serious adverse event in eight of the 266 patients receiving the aprepitant regimen, compared to two of the 251 patients in the corresponding standard therapy group. The incidence of anemia, febrile neutropenia and thrombocytopenia were generally similar between treatment groups with a difference between treatment groups less than 1%.<sup>1</sup>

Overall, the Medical Officer's summary concluded, "analysis of adverse events of individual chemotherapeutic agents did not identify a definite signal. There were small differences in the incidence of infection and hematologic adverse events that may represent a signal. The number of patients studied was too small to draw any definite conclusions."<sup>1</sup>

### **Known Drug Interactions**

During phase IIb clinical trials a drug-drug interaction was identified between aprepitant and dexamethasone that resulted in the adjustment of dexamethasone doses in patients who received aprepitant during phase III trials. When aprepitant 125 mg was coadministered with dexamethasone 20 mg orally on day 1, followed by aprepitant 80 mg/d plus dexamethasone 8 mg/d orally on days 2–5, dexamethasone's AUC increased by 2.2-fold, on days 1 and 5.<sup>2</sup> Oral dexamethasone doses should be reduced by approximately 50% when coadministered with aprepitant, to achieve dexamethasone exposures similar to those obtained when it is given without aprepitant.<sup>2</sup> It was also noted that febrile neutropenia and serious infections occurred more frequently among patients who received aprepitant in a dexamethasone-containing regimen than standard prophylaxis containing dexamethasone. Merck

& Co., Inc., has attributed these adverse events to an increased exposure to dexamethasone among aprepitant-treated patients.<sup>1</sup>

Aprepitant 125 mg PO plus methylprednisolone 125 mg IV on day 1, followed by aprepitant 80 mg/d PO plus methylprednisolone 40 mg/d PO on days 2–3, increased the methylprednisolone AUC by 1.34-fold on day 1, and by 2.5-fold on day 3. Intravenously-administered methylprednisolone doses should be decreased by approximately 25%, and oral doses should be decreased by approximately 50% when coadministered with aprepitant to achieve methylprednisolone exposures similar to those obtained when it is given without aprepitant.<sup>2</sup>

Aprepitant 100 mg/d PO for 14 d with an oral contraceptive containing ethinyl estradiol 35 µg and norethindrone 1 mg, decreased the AUC of ethinyl estradiol and norethindrone by 43% and 8%, respectively. Although the 3-day aprepitant regimen given concomitantly with oral contraceptives has not been studied, patients should be advised to use alternative or back-up methods of contraception.<sup>2</sup>

Aprepitant has been shown to significantly increase the AUC of known CYP3A4 substrates such as midazolam and diltiazem.<sup>2</sup> In addition, ketoconazole, a potent CYP3A4 inhibitor was shown to significantly increase the AUC and mean terminal  $t_{1/2}$  of aprepitant.<sup>2</sup> Rifampin, a potent inducer of CYP3A4, was shown to decrease aprepitant AUC by ~11-fold and in mean terminal  $t_{1/2}$  by ~3-fold.<sup>2</sup>

Aprepitant is also an inducer of CYP2C9.<sup>2</sup> The ratio of International Normalized Ratio (INR) decreased by about 11% from baseline on day eight following concomitant administration of aprepitant 125-mg aprepitant on day 1 and 80 mg/d on days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. In patients on chronic warfarin therapy who receive aprepitant prophylaxis with emetogenic chemotherapy, the INR should be closely monitored during the 2-week period after first exposure to aprepitant, particularly at 7–10 days, after initiation.<sup>2</sup> Aprepitant was also shown to decrease the AUC of tolbutamide, another substrate for CYP2C9.<sup>1</sup> Coadministration of aprepitant with other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in decreased plasma concentrations of those drugs.<sup>2</sup>

Coadministration of aprepitant tablets once daily, comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in both aprepitant and paroxetine AUC by ~25% and  $C_{max}$  by ~20%.<sup>2</sup> Paroxetine is a known substrate and inhibitor of CYP2D6.

### Precautions and Contraindications

#### Pediatric Patients

Aprepitant pharmacokinetics have not been adequately evaluated in patients less than 18 years of age.<sup>2</sup>

#### Hepatic Insufficiency

Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Clinical and pharmacokinetic data are not available for patients with severe hepatic insufficiency (Child-Pugh score >9).<sup>2</sup>

#### Renal Insufficiency

Aprepitant dose adjustment is not necessary for patients with renal insufficiency and for patients with end-stage renal disease who receive hemodialysis.<sup>2</sup>

#### Pregnancy and Teratogenic Effects

Category B. Teratology studies performed in rats have revealed no evidence of impaired fertility or fetal harm due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aprepitant should be used during pregnancy only if clearly needed.<sup>2</sup>

#### Nursing Mothers

Aprepitant is excreted in the milk of rats. It is not known whether it is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.<sup>2</sup>

#### Dosage and Administration

The FDA approved dosing regimen for aprepitant is a three-day regimen in combination with a glucocorticoid and a 5-HT<sub>3</sub> antagonist. The recommended dose of aprepitant is 125 mg orally 1 hour prior to chemotherapy treatment and 80 mg/d on the next two consecutive days. Aprepitant has not been studied for the treatment of established nausea and vomiting.<sup>2</sup> Aprepitant may be taken with or without food. Chronic continuous aprepitant use for prevention of nausea and vomiting is not recommended because it has not been studied, and because the onset of cytochrome P450 enzyme induction characteristically occurs more slowly than inhibition, aprepitant's drug interaction profile may change during chronic continuous use.<sup>2</sup>

#### Cost

The cost of aprepitant to the Clinical Center Pharmacy Department as of May 2003:

Emend® 125-mg capsules cost \$64.56/capsule

Emend® 80-mg capsules cost \$59.42/capsule

The cost of a three-day course of aprepitant using the FDA-approved dosing regimen is \$183.40.

#### Conclusion

Please refer to the recommendations and guidelines for use of aprepitant (beginning on page one).

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