

Initial Public Comment for
Aprepitant for Chemotherapy-Induced Emesis
CAG-00248N
July 6 – August 6, 2004

Commenter: Duncan, Sariah, RN, BSN, OCN

Organization:

Date: August 2, 2004

Comment:

Please Do Not Limit Anti-Emetic Coverage!!

I don't think Emend should be considered full replacement for other covered treatments for chemotherapy induced emesis. On the few patients who it was prescribed to in our clinic, it did not always work well. We find that we still have to give the patient IV anti-emetics, even if they took Emend, because they still throw up.

Commenter:

Takahashi, Gary

Organization:

Oregon Hematology Oncology Association

Date:

August 6, 2004

Comment:

In my experience, Emend (aprepitant) is useful only as an adjunct to other antiemetics to prevent delayed-onset nausea and vomiting. It is only mildly effective when given alone, and must be combined with more potent anti-emetics to control acute-onset nausea. I recommend against using Emend as an oral substitute for drugs such as granisetron or palonosetron.

Commenter: D'Emanuele, Ross
Organization: Dorsey & Whitney, LLP
Date: August 6, 2004
Comment:

**Public Comment Offered in Response to
CMS' National Coverage Analysis (NCA) Titled
"Aprepitant for Chemotherapy-Induced Emesis" (CAG-00248N)**

POSITION

Oral EMEND® is *not* a replacement for any current commercially available intravenous antiemetic in the United States. Therefore, it is not appropriate to reimburse it as a Medicare Part B benefit. EMEND needs to be administered in conjunction with a 5-HT₃ receptor antagonist and is not stand alone therapy. It does not function as a prodrug or have an IV equivalent. EMEND may be an appropriate drug to receive coverage under the Part D Medicare Prescription Drug Benefit to be implemented in 2006.

BACKGROUND

In the above referenced NCA, CMS has asked for public comment regarding an internally generated request for a National Coverage Decision for reimbursement of oral EMEND® (aprepitant) for the prevention of chemotherapy-induced nausea and vomiting. This CMS request for public comment prior to implementing changes in the National Coverage Determination process is now required by Section 731(c) of the Medicare Prescription Drug Improvement and Modernization Act of 2003. As an initial matter, Section 4460 of the Medicare Carriers Manual states that in order for any oral anti-emetic drug to be covered by Medicare, the drug must be provided "as full therapeutic replacement for an intravenous anti-emetic drug as part of a cancer chemotherapeutic regimen." This public

comment will provide CMS with information to show that oral EMEND is *not* a replacement for any current commercially available intravenous antiemetic in the United States and should *not* be reimbursed by the Medicare Program.

Oral EMEND was approved by the United States Food and Drug Administration (FDA) on March 26, 2003. The current label for EMEND states it is “indicated, in combination with other antiemetics, for the prevention of chemotherapy-induced nausea and vomiting (CINV) after initial and repeat cycles of highly-emetogenic chemotherapy including cisplatin.”¹ According to the approved label, EMEND is “administered for three days as part of a regimen that includes a corticosteroid and a 5-HT₃ receptor-antagonist.” The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment on day 1 followed by 80 mg orally in the morning on days 2 and 3 after chemotherapy. EMEND is not available in an intravenous formulation, and as a single agent, oral EMEND is not as effective as commercially available 5HT₃ receptor-antagonists, ondansetron, granisetron, dolasetron or palonosetron in prevention of CINV.²⁻⁶

The FDA approval of EMEND was based on 2 pivotal, parallel, double-blind, controlled trials in patients receiving a highly emetogenic chemotherapy (HEC) regimen that included cisplatin, comparing the aprepitant regimen (aprepitant, dexamethasone, and ondansetron) with standard therapy (ondansetron and dexamethasone) (Table 1).^{7,8} Complete response (no emesis and no use of rescue therapy) was evaluated during the acute (0-24 hr), delayed (25-120 hrs) and overall (0-120 hrs: primary endpoint) time intervals. In both studies, adding aprepitant to standard therapy was superior to standard therapy alone (Figures 1 and 2).

Table 1: Treatment Regimens: Aprepitant Pivotal Trials

Group	Day 1			Days 2-3		Day 4
	O	D	A	D	A	D
Aprepitant	32 mg	12 mg	125 mg	8 mg	80 mg	8 mg
Standard Therapy	32 mg	20 mg	P	16 mg	P	16 mg

O = ondansetron, D = dexamethasone, A = aprepitant, P = placebo

At the recent ASCO 2004 meeting, results of a large phase 3 trial evaluating the efficacy of a modified aprepitant regimen (same as HEC trials but with only a single day (Day 1) of dexamethasone) versus a similarly modified standard regimen (3 days ondansetron with Day 1 only of dexamethasone) in patients with breast cancer receiving moderately emetogenic chemotherapy (MEC) were presented (Figure 4).⁹ Unexpectedly, the magnitude of the difference between the aprepitant regimen and standard therapy seen in the HEC trials was much less in this MEC trial. Furthermore the CR rate for patients receiving aprepitant in the delayed setting was not significantly different from that of the ondansetron treated group $P > 0.05$, raising concerns about the value of this agent in the setting outside of high-dose cisplatin.

Figure 2: Aprepitant Pivotal Registration Trial 052: Complete Response

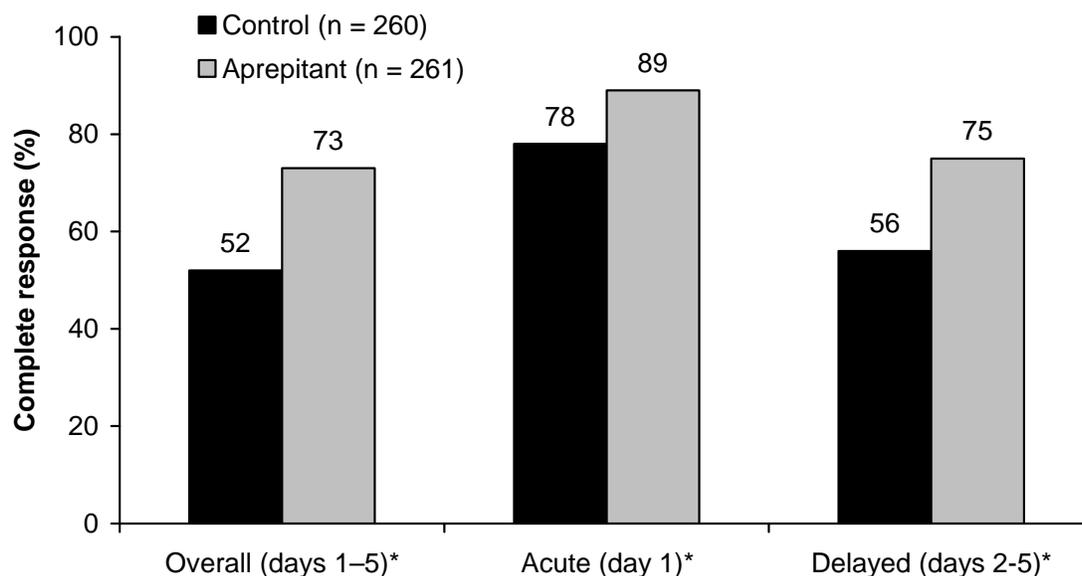
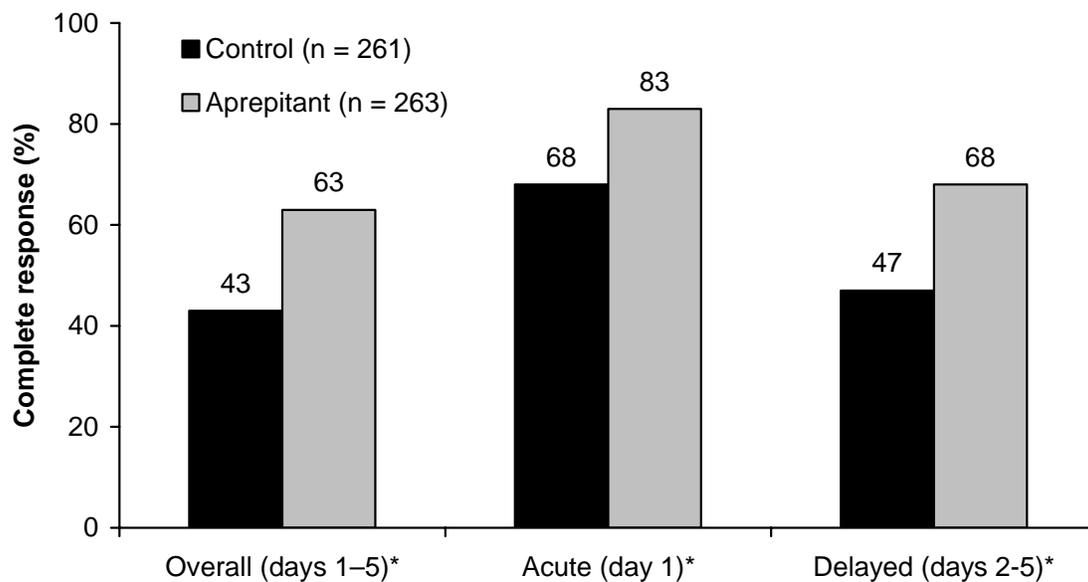
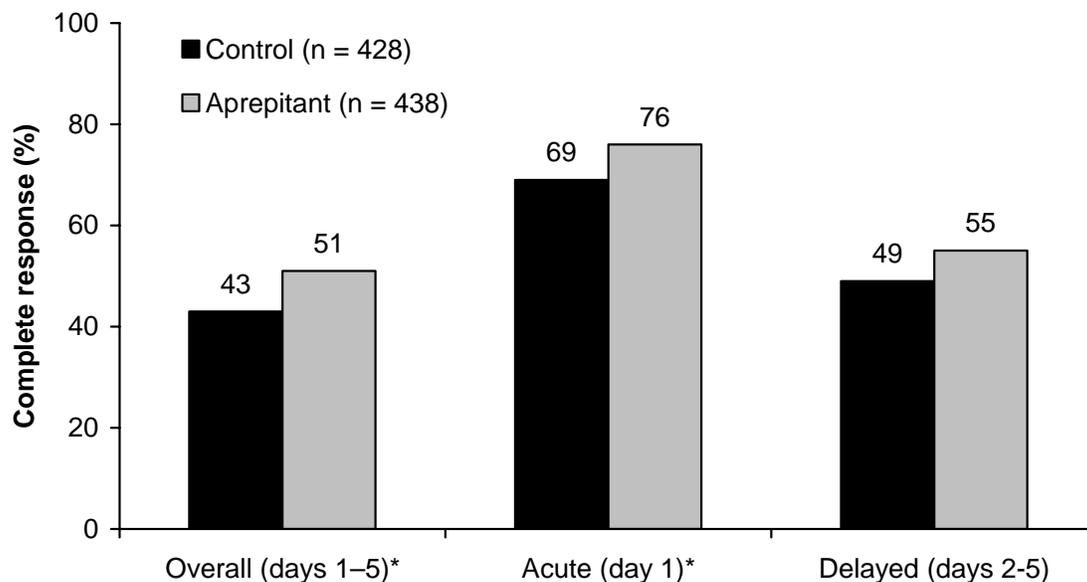


Figure 3: Aprepitant Pivotal Registration Trial 054: Complete Response



*** p < 0.001**

Figure 4: Aprepitant Trial in Patient Receiving Moderately Emetogenic Chemotherapy: Complete Response



* $p < 0.05$

PUBLISHED EVIDENCE TO SUPPORT THE POSITION STATEMENT

EMEND (aprepitant) belongs to the class of drugs known as NK-1 receptor antagonists.¹⁰⁻

¹² To date, almost all published clinical trials that have been conducted with NK-1 receptor antagonists have been in patients receiving highly-emetogenic chemotherapy with high dose cisplatin. One of the key observations from the first reported clinical trial of the NK-1 receptor antagonists in CINV suggested that NK-1 receptor antagonists alone were not adequate to control acute CINV. Kris et al¹³ (Table 2, study 1) evaluated CP 122,721 in 17 cancer patients receiving cisplatin ($\geq 80\text{mg/m}^2$ over $< 3\text{hours}$). A single dosage (50 mg [n=3], 100mg [n=4] and 200mg [n=10]) was administered 30 minutes pre-cisplatin. Ten of the 17 patients also received serotonin antagonists and dexamethasone. This first clinical trial in human subjects strongly suggested that NK-1 receptor

antagonists alone were not adequate to control emesis in the acute phase but could have a significant contribution to improving control when added to a 5HT₃-receptor antagonist.

In a trial of an earlier formulation of aprepitant, Van Belle et al¹⁴ (Table 2, study 2) conducted a double blind, randomized study in 176 cisplatin-naïve patients. All patients received IV dexamethasone 20 mg pre-cisplatin. Group 1 (n=61) received a single dose of the IV NK-1 prodrug L-758,298 (100 mg) pre-cisplatin followed by its oral formulation, L-754,030 (300 mg) on day 2 to 5. Group 2 (n=58) received IV L-758,298 (100mg) on day 1 pre-cisplatin followed by placebo on day 2 to 5. Group 3 (n=57) received ondansetron (32mg) pre-cisplatin followed by placebo in day 2 to 5. This study supports the notion that acute emesis in patients receiving high dose cisplatin appears to be a serotonin-mediated phenomenon whereas delayed emesis is not entirely mediated by serotonin mechanisms.

In another multicenter, double blind, randomized study Navari¹⁵ (Table 2, study 3), evaluated the effect of an earlier formulation of oral aprepitant, L-754, 030 on acute and delayed emesis, in 159 patients receiving a single dose of cisplatin (> 70mg/m²). All patients were given granisetron 10mcg/kg IV and dexamethasone 20 mg IV pre-cisplatin and randomized to one of 3 treatment arms. Group 1 received oral L-754,030 400 mg pre-cisplatin then 300mg from days 2 to 5, Group 2 received oral L-754,030 400 mg pre-cisplatin and placebo on days 2 to 5, and group 3 served as the control group receiving placebo pre-cisplatin and days 2 to 5. This study demonstrated the effectiveness of L-754, 030 in preventing delayed emesis and confirmed that aprepitant was additive to

standard therapy with a 5HT3 receptor antagonist and dexamethasone thereby improving control of acute emesis.

In another multicenter double blind randomized trial of 351 cisplatin-naïve patients, Campos et al¹⁶ (Table 2, study 4) evaluated treating patients with MK-869 (aprepitant-the oral formulation of L-758,298), the day prior to chemotherapy (Day minus 1) compared to placebo and then randomized patients to one of four treatment groups. All patients received dexamethasone 20 mg orally prior to cisplatin. The MK-869 containing regimens (Groups 2, 3, and 4) all performed better than placebo in the delayed emesis phase.

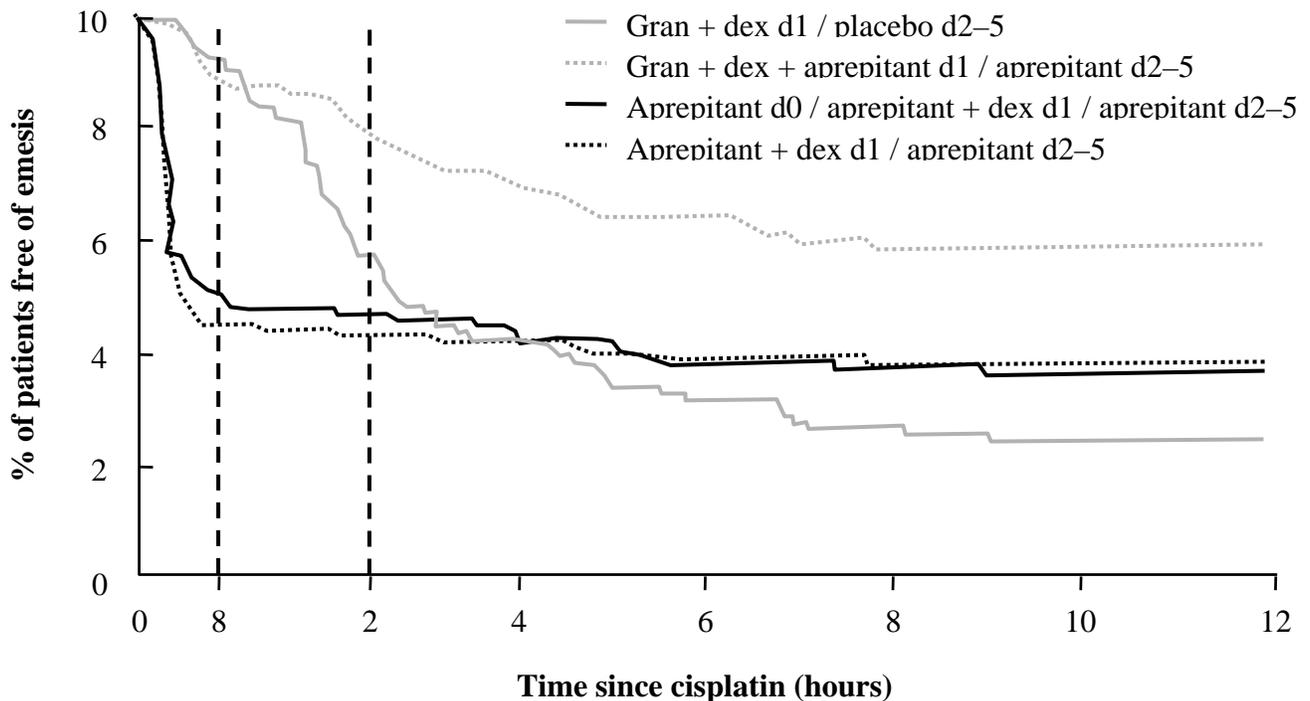
Table 2: Summary of NK1 Trials

1. Study	Treatment	II. Number pts	III. Complete Response	
			Acute	Delayed
1. Kris	CP122,721	7	15%	86%
	CP122,721 + 5HT3 + dex	10	100%	80%
<i>Conclusion: 5-HT₃ critical in acute phase, NK1 monotherapy is ineffective for acute but NK1 plays role in delayed phase</i>				
2. Van Belle	Group 1: Day 1: dex + L-758,298 Days 2-5: L-754-030	61	50%	68%
	Group 2: Day 1: dex + L-758,298 Days 2-5: placebo	58	47%	63%
	Group 3: Day 1: dex + OND Days 2-5: placebo	57	84%	41%
<i>Conclusion: 5-HT₃ critical in acute phase, NK1 additive to 5-HT₃ + dex for acute and delayed emesis</i>				
3. Navari	Group 1: Day 1: GRAN + dex + L-754,030 Days 2-5: L-754-030	Total n = 159	93%	52%
	Group 2: Day 1: GRAN + dex + L-754,030 Days 2-5: placebo		94%	43%
	Group 3: Day 1: GRAN + dex Days 2-5: placebo		67%	16%
A. <i>Conclusion: NK1 additive to 5-HT₃ + dex for acute and delayed emesis</i>				
4. Campos	Group 1: Day 1: GRAN + dex + placebo Days 2-5: placebo	Total n = 351	57%	29%
	Group 2: Day 1: GRAN + dex + MK-869 Days 2-5: MK-869		80%	63%
	Group 3: Day 1: Placebo + dex + MK-869		46%	51%

	Days 2-5: MK-869 Group 4: Day 1: placebo + dex + MK-869 Days 2-5: MK-869		43%	57%
Conclusion: 5-HT ₃ critical for acute phase; NK1 additive to 5-HT ₃ + dex for acute and delayed emesis				

The time course of emesis in this trial was published by Hesketh et al¹⁷ and clearly demonstrates that aprepitant as a single agent is inadequate as an effective antiemetic for preventing acute CINV in patients receiving highly-emetogenic chemotherapy such as cisplatin (Figure 3).

Figure 3: Time Course of Emesis Following Cisplatin with a 5-HT₃ Receptor Antagonist or Aprepitant



SAFETY

There are numerous concerns about drug-drug interactions with aprepitant as indicated on the FDA label for EMEND.

Contraindications

EMEND® (aprepitant), is a moderate CYP3A4 inhibitor. EMEND should not be used concurrently with pimozone, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. EMEND is contraindicated in patients who are hypersensitive to any component of the product.

Precautions

Drug Interactions

Aprepitant is a substrate, a moderate inhibitor and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND® (aprepitant), to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone.

CONCLUSION:

As all the trials evaluating the NK1 antagonists, including aprepitant, clearly indicate that it must be administered in conjunction with a 5-HT₃ receptor antagonist and dexamethasone, it is clearly *not* a replacement for any current commercially available

intravenous antiemetic in the United States, but rather, “add-on” therapy. Therefore, it is not appropriate to reimburse it as a Medicare Part B benefit as stated in Pub. 100-4, Medicare Claims Processing Manual, Chapter 17, Section 80.2.

References

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Commenter: Senich, Barbara A.
Organization: Roche Laboratories, Inc.
Date: August 6, 2004
Comment:

(See next page)



Pharmaceuticals

August 6, 2004

Marc Stone, MD
Lead Medical Officer
Gay W. Burton
Lead Analyst
Centers for Medicare and Medicaid Services
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Dear: Dr. Stone and Ms. Burton:

**Re: Comments of Roche Laboratories Inc. ("Roche")
National Coverage Analysis: Aprepitant for Chemotherapy-Induced Emesis
(CAG-00248N)**

Roche Laboratories Inc, a research based pharmaceutical company (hereinafter "Roche"), offers the following comments to CMS regarding the National Coverage Analysis: Aprepitant for Chemotherapy-Induced Emesis (CAG-00248N). We are concerned that it would be both clinically unwise and contrary to law to provide coverage of Emend® (aprepitant) that would in any way displace current coverage of anti-emetics.

Chemotherapy-induced nausea and vomiting (CINV) is caused by a complex combination of pathways and neurotransmitter receptors. For this reason, despite the availability of numerous drugs to treat CINV, no one product can fully assist all patients with this debilitating problem. Thus, Roche supports the use of various drugs to treat CINV, including the continued availability of 5-HT₃ receptor antagonists, and – to the extent permitted by law – use of Emend as indicated in labeling, (*i.e.*, only in combination with other antiemetic agents for highly emetogenic cancer chemotherapy). With respect to the above-referenced National Coverage Analysis, however, Roche believes that CMS should carefully consider all of the clinical, public policy and legal challenges associated with a displacement – in whole or in part- of current anti-emetic products. Specifically, we believe:

- The Centers for Medicare and Medicaid Services' (CMS) legal authority to cover Emend under Medicare Part B is questionable because statute provides coverage for oral anti-emetic drugs as *full therapeutic replacements for intravenous dosage forms*.

Emend, as approved, is not a “full replacement” for any currently covered anti-emetic products;

- Emend is FDA approved for use only in combination with other anti-emetic agents for the prevention and treatment of CINV and lacks clinical support for use as a sole antiemetic agent;
- CMS should carefully consider the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Antiemesis and the Multinational Association for Supportive Care in Cancer (MASCC) Antiemetic Guidelines, neither of which consider Emend a full replacement for other anti-emetic products; and
- Emend can not be a replacement for covered drugs currently available to Medicare Part B beneficiaries because physicians must proceed with caution when prescribing Emend to patients receiving concomitant therapies, including chemotherapy agents that are primarily metabolized through CYP3A4.

Accordingly, we respectfully suggest that CMS reconsider the above referenced national coverage analysis.

Introduction

Emend is an orally administered, centrally acting antiemetic with no intravenous equivalent that works as a competitive antagonist of the neurokinin₁ (NK-1) receptor.¹ Generally, NK-1 receptor antagonists prevent emesis induced by the chemotherapeutic agent cisplatin, and other highly emetogenic chemotherapeutic agents.² Aprepitant demonstrates modest efficacy in reducing nausea and vomiting in the acute and delayed phases following administration of moderately emetogenic chemotherapeutic agents.

Approving Emend as a “replacement” – in whole or in part – for currently covered anti-emetic products will represent a step backward for the treatment of chemotherapy-induced nausea and vomiting in its acute, delayed, and anticipatory phases. Based upon the current products available, cancer patients may need to be treated with multiple anti-emetic therapies. Currently, nearly 60% of patients experience nausea and 30% experience vomiting in the days after their first course of cancer chemotherapy.³ CINV is a complex condition that may require the use of multiple products. If CMS limits the existing available anti-emetic products, it will exacerbate the adverse effects currently experienced by cancer patients.

In addition to the clinical consequences of this action, the Agency’s legal authority to cover Emend under Medicare Part B is questionable. Medicare Part B coverage is generally limited to drugs or biologics administered by infusion or injection; however, Section 4557 of the Balanced Budget Act of 1997 provides coverage for oral anti-emetic drugs as *full therapeutic replacements for intravenous dosage forms* as part of a chemotherapeutic regimen. Further, the CMS Supplier Manual provides coverage for oral anti-emetic drugs “when used as full

¹ Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK₁ receptor antagonist MK-0869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. *Neuropharmacology*. 2000;39:652-63.

² Id.

³ Morrow GR, Roscoe JA, Hickok JT, et al. Initial control of chemotherapy-induced nausea and vomiting in patient quality of life. *Oncology* 1998;12 (suppl 4):32-37.

replacement for the *intravenous (IV) form of the same drug* during chemotherapy treatment.”⁴ Aprepitant does not contain the same active ingredient found in currently covered chemotherapy induced anti-emesis agents under Medicare Part B, and Emend does not meet this statutory definition of a full replacement drug. As such, CMS does not appear to have the legal authority to cover Emend under Medicare Part B as contemplated under this NCA. Beyond the questionable legal authority, CMS may also consider the effect of issuing a new coverage determination for a product which arguably should be covered under the new Medicare Part D benefit. If CMS broadens its Part B coverage policy at the same time similar products are expected to be administered under the new Part D benefit, it would send a confusing message regarding the mechanism by which drugs will be placed into either Part B or Part D.

Emend Is Approved for Use Solely In Combination with other Anti-Emetics

According to the approved label and package insert, “EMEND, *in combination with other antiemetic agents*, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.”⁵ The indication is noteworthy because it requires that Emend be used in combination with additional anti-emetic agents. If the CMS inappropriately determines aprepitant is a “full replacement” for currently covered anti-emetic products, it is unclear that Emend will then be prescribed consistent with its FDA approved labeling.

In numerous studies, Emend has been shown to provide statistically significant additional protection from acute and delayed nausea and vomiting, when provided in combination with a 5-HT₃ inhibitor, plus dexamethasone. Thus, any CMS action to limit the availability of either 5-HT₃ inhibitor plus dexamethasone would be misguided. Specifically, in a double-blind placebo-controlled study (n = 351), a triple combination of oral aprepitant, granisetron (5-HT₃), and dexamethasone (Corticosteroid) before cisplatin was superior to dual treatment with granisetron plus dexamethasone or aprepitant alone in preventing acute vomiting in cisplatin-naive solid-tumor patients. These findings clearly support the need for use of numerous anti-emetic products, with Emend clearly being an additive to, but not a replacement for, existing covered therapies.

If the Centers for Medicare and Medicaid Services (CMS) inappropriately determines Emend is a “replacement” – in whole or in part – for currently covered anti-emetic products, chemotherapy-induced nausea and vomiting in its acute, delayed, and anticipatory phases will remain one of the most problematic treatment related adverse effects for cancer patients in the Medicare population. Limiting the currently available anti-emetic products will exacerbate the adverse effects currently experienced by cancer patients, including the possibility of serious clinical adverse events such as dehydration and electrolyte imbalance, and may require remedial treatment including intravenous hydration and possibly hospitalization.

Chemotherapy-Induced Nausea and Vomiting

Chemotherapy is known to induce emesis, in part, by causing enterochromaffin cells lining the gastrointestinal tract to release serotonin in response to cell damage. Serotonin binds to vagal afferent 5-HT₃ receptors in the gastrointestinal tract, which send impulses to the vomiting center. The chemoreceptor trigger zone (CTZ) has an important role in

⁴ CMS Intermediary Manual, Secin 3660.15, Oral Anti-Nausea Drugs as Full Therapeutic Replacements for Intravenous Dosage Forms As Part of a Cancer Chemotherapeutic Regimen, *available at* http://www.cms.hhs.gov/manuals/13_int/a3660.asp#_1_14

⁵ Emphasis added

chemotherapy-induced emesis because it lies outside the blood-brain barrier, which makes it accessible to circulating emetogenic substances.⁶

CINV is generally divided into three phases: acute, delayed, and anticipatory. Acute chemotherapy-induced nausea and vomiting includes symptoms that develop within one to four hours and last up to 24 hours after a dose of cancer chemotherapy. Acute CINV typically produces the most severe emesis after chemotherapy administration as compared with delayed CINV. Delayed chemotherapy-induced nausea and vomiting (also called delayed emesis) develops 24 to 72 hours after the patient receives chemotherapy, and may last for several days. The cause of delayed CINV is complex and may involve several different neurotransmitters. Delayed CINV is believed to lead to the third phase of CINV - anticipatory nausea and vomiting. Specifically, anticipatory nausea and vomiting generally occurs prior to subsequent cycles of chemotherapy after patients have experienced CINV. Between 10% and 44% of patients experience anticipatory CINV by their fourth treatment cycle.

Treatment of CINV

Four major classes of antiemetic agents are used to treat the acute and delayed phases of CINV: (1) corticosteroids; (2) D2 receptor antagonists; (3) 5-HT₃ receptor antagonists; and (4) NK-1 receptor antagonists. Corticosteroids antiemetic mechanism of action is unclear, but they may work through prostaglandin antagonism, tryptophan depletion, or changes in the permeability of the cerebrospinal fluid to serum proteins.⁷ The adverse effects of corticosteroids used to prevent CINV are primarily gastrointestinal upset, anxiety, and insomnia. Unless contraindicated, corticosteroids should be part of any regimen for prevention of CINV.⁸ Dopamine-2 receptor antagonists work centrally to block dopamine receptors in the CTZ and the vomiting center. Adverse effects associated with D2 receptor antagonists include sedation, CNS depression, restlessness, and extrapyramidal symptoms.⁹

The 5-HT₃ receptor antagonists have the unique benefit of acting at central and peripheral sites by binding to 5-HT₃ receptors found in the CTZ and afferent pathways of the gastrointestinal tract.¹⁰ Oral and intravenous doses of 5-HT₃ receptor antagonists can generally be used interchangeably, depending on patients' needs. The most common adverse effects of these agents are mild headache, constipation, and asymptomatic prolongation of ECG intervals.¹¹

The NK-1 receptor antagonists are a new class of drugs, of which Emend is the only approved agent. Aprepitant crosses the blood-brain barrier to block NK-1 receptors and augments the antiemetic efficacy of 5-HT₃ receptor antagonists and dexamethasone, particularly in the setting of delayed CINV caused by highly emetogenic chemotherapeutic agents.¹² The most

⁶ Hesketh PJ, Gandara DR. Serotonin antagonists: a new class of antiemetic agents. *J Natl Cancer Inst* 1991;83:613-620.

⁷ Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. *Drug Saf* 003;26:227-259.

⁸ Id.

⁹ ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. *Am J Health Syst Pharm* 1999;56:729-764.

¹⁰ Id.

¹¹ Aloxi® (palonosetron HCl injection). Prescribing information. Bloomington, Minn: MGI Pharma Inc; July 2003.

¹² Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al, for the Aprepitant Protocol 054 Study Group. Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America.

common adverse effects in clinical studies were diarrhea, dizziness, nausea, mild anorexia, and drug interactions via inhibition and induction of the CYP3A4 enzyme pathway.¹³

NCCN Guidelines and MASCC Guidelines Do Not Support the Proposed Change

In determining whether aprepitant is a full or partial replacement for available anti-emetic products, CMS should consider the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Antiemesis¹⁴ and the Multinational Association for Supportive Care in Cancer (MASCC) Antiemetic Guidelines¹⁵. Under to the NCCN Guidelines, Emend should not be administered alone but rather, “as per the labeled indication aprepitant should be administered 125 mg orally one hour prior to chemotherapy on day one, along with a 5-HT₃ receptor antagonist and dexamethasone.” Similarly, the MASCC guidelines state that a combination of products is necessary to limit nausea and vomiting following chemotherapy. Specifically, the guidelines state that “to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT₃ antagonist, dexamethasone, and aprepitant given before chemotherapy is recommended.” Following the guidelines of NCCN and MASCC that multiple products are necessary to effectively eliminate nausea and vomiting, CMS should not limit the current products available to physicians treating patients suffering from CINV.

Antiemetic Drug Interaction

As noted in the Emend package insert, physicians must proceed with caution when prescribing Emend to patients receiving concomitant therapies, including chemotherapy agents that are primarily metabolized through CYP3A4.¹⁶ Specifically, the package insert reads “due to the small number of patients in clinical studies who received the CYP3A4 substrates docetaxel, vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied.” Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of Emend on the pharmacokinetics of orally administered CYP3A4 substrates may be greater than the effect of Emend on the pharmacokinetics of intravenously administered CYP3A4 substrates. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, Emend was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

Conclusion

A favorable coverage decision for Emend under Medicare Part B would be both novel and potentially precedent-setting for entry of numerous other products that have not been able to be covered under Part B due to the Agency’s long-standing requirements cited above. As detailed above, other than use in combination with other antiemetic agents, the full or partial replacement with Emend of currently-covered drugs for CINV is contrary to product labeling, good clinical practice, and current law. Roche appreciates the opportunity to submit

Cancer 2003;97:3090–3098.

¹³ Van Belle S, Lichinitser MR, Navari RM, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. *Cancer* 2002;94:3032-3041.

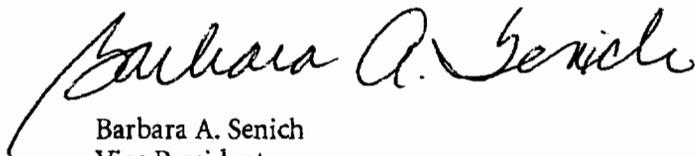
¹⁴ See http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

¹⁵ See http://www.mascc.org/index.php?load=pro_resources&page=index&cat_id=1

¹⁶ See: http://www.fda.gov/cder/foi/label/2003/21549_Emend_lbl.pdf. Accessed November 4, 2003.

comments on this important issue. We would welcome the opportunity to discuss these issues further or answer any questions you might have on this submission.

Respectfully submitted,



Barbara A. Senich
Vice President
Marketing & Sales Services
Roche Laboratories Inc.
340 Kingsland Street
Nutley, NJ 07110

Enclosures: (To be provided with hard copy submission)



August 16, 2004

Gay W. Burton
Lead Analyst
Centers for Medicare and Medicaid Services
National Coverage Analysis
7500 Security Blvd.
Mailstop C1-1114
Baltimore, MD 21244-1850

Dear Ms. Burton:

Enclosed please find supplemental information to the August 6, 2004, submission made by Roche Laboratories Inc. ("Roche"). After the submission, it was discovered that the references were inadvertently misidentified at the bottom of the pages within the letter.

In order to rectify this administrative error, please accept the following information contained in the enclosed binder:

- A. Copy of the August 6, 2004, letter
- B. Corrected list of all references
- C. Referenced documents

Again, please accept my apology for the miscue with the references. Should you have any questions or comments, please do not hesitate to contact me.

Sincerely,

A handwritten signature in black ink that reads "Nimish Shah".

Nimish Shah

Enclosures
NS/jw

**References to August 6, 2004 Submission from Roche Laboratories Inc.
 (“Roche”) on National Coverage Analysis: Aprepitant for
 Chemotherapy-Induced Emesis (CAG- 00248N)**

Reference	Reference Name
#1	Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al, for the Aprepitant Protocol 054 Study Group. Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America.
#2	Emend Package Insert, Emend (Aprepitant) Prescribing Information, Merck & Company, Whitehouse Station, NJ
#3	Morrow GR, Roscoe JA, Hickok JT, et al. Initial control of chemotherapy-induced nausea and vomiting in patient quality of life. <i>Oncology</i> 1998;12 (suppl 4):32-37
#4	CMS Intermediary Manual, Secin 3660.15, Oral Anti-Nausea Drugs as Full Therapeutic Replacements for Intravenous Dosage Forms As Part of a Cancer Chemotherapeutic Regimen, <i>available at</i> http://www.cms.hhs.gov/manuals/13_int/a3660.asp#_1_14
#5	Emend Package Insert, Emend (Aprepitant) Prescribing Information, Merck & Company, Whitehouse Station, NJ
#6	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. <i>AM J Health Syst Pharm</i> 1999;56:729-764
#7	Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. <i>Drug Saf</i> 003;26:227-259.
#8	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. <i>AM J Health Syst Pharm</i> 1999;56:729-764
#9	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. <i>AM J Health Syst Pharm</i> 1999;56:729-764
#10	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. <i>AM J Health Syst Pharm</i> 1999;56:729-764

#11	ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. AM J Health Syst Pharm 1999;56:729-764
#12	Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al, for the Aprepitant Protocol 054 Study Group. Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America.
#13	Emend Package Insert, Emend (Aprepitant) Prescribing Information, Merck & Company, Whitehouse Station, NJ / Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al, for the Aprepitant Protocol 054 Study Group. Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America.
#14	NCCN Clinical Practice Guidelines See http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf
#15	MASCC Clinical Guidelines See http://www.mascc.org/index.php?load=pro_resources&page=index&cat_id=1
#16	Emend Package Insert, Emend (Aprepitant) Prescribing Information, Merck & Company, Whitehouse Station, NJ

Commenter: Gershon, Barry
Organization: GlaxoSmithKline
Date: August 6, 2004
Comment:

GlaxoSmithKline (GSK) appreciates the opportunity to comment on the National Coverage Analysis (NCA –CAG—00248N)) to explore whether it would be appropriate for the Medicare program to provide Medicare coverage for aprepitant, trade name Emend. That notice states that CMS would be expected to make a decision regarding coverage in April 2005, with, presumably, implementation somewhat later.

The prescribing information approved by the **Food and Drug Administration (FDA)** states that aprepitant, “in combination with other anti-emetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high dose cisplatin.” Unlike some other anti-emetic agents, aprepitant does not have an indication for prevention or treatment of post operative nausea and vomiting. The comments below suggest that there is no data to support a conclusion that aprepitant is a “full replacement” for intravenous therapies to treat chemotherapy induced nausea and vomiting and, thus, CMS should not extend coverage under Part B.

GSK is a multinational drug company, formed in 2001 through the merger of GlaxoWellcome and SmithKline Beecham and has significant experience with anti-emetic therapy. Prior to the merger, Glaxo Wellcome marketed *Zofran* (ondansetron HCl) and SmithKline Beecham marketed *Kytril* (granisetron HCl). Since the merger, the combined company markets *Zofran*, having divested ownership of *Kytril*. In fact, both legacy companies were actively involved with the drafting and eventual passage of the legislation that first established Medicare coverage for oral anti-emetics. We are hopeful that our involvement with anti-emetic therapies and with the passage of the legislation that allowed select Part B coverage of oral anti-emetics will be helpful to CMS as the agency evaluates potential coverage options for aprepitant.

While GSK continues to support Medicare coverage for all therapies to treat cancer patients that qualify under Medicare policies, we also understand the importance of coverage decisions that are consistent with Medicare statutory and regulatory policies, as well as in the best interest of Medicare patients. Based on our experience with and understanding of the original legislation and our review of clinical data, GSK believes that it would not be appropriate to provide Part B coverage for aprepitant. Instead, GSK believes that, given current law, it would be appropriate to allow for the immediate inclusion of aprepitant under the current Medicare discount card program and for coverage under Part D, when the program is implemented in 2006.

EXECUTIVE SUMMARY

Our rationale is summarized as follows:

1. Aprepitant does not meet the statutory standard as a “full replacement for the anti-emetic therapy which would otherwise be administered intravenously”.
2. There is not sufficient scientific evidence at this time that supports aprepitant’s safety and effectiveness as a full replacement therapy in Medicare patients,
3. CMS can achieve congressional policy goals by extending coverage to aprepitant under Medicare Part D as per the recent Medicare Modernization Act.

OVERVIEW OF MEDICARE COVERAGE FOR ORAL ANTI-EMETICS

Coverage of oral anti-emetics was enacted into law under Section 4557 of the Balanced Budget Act (BBA) of 1997 (Public Law 105-33). More specifically, for services furnished on or after January 1, 1998, the BBA added coverage under Section 1861(s)(2) of the Social Security Act for

"an oral drug (which is approved by the Federal Food and Drug Administration) prescribed for use as an acute anti-emetic used as part of an anticancer chemotherapeutic regimen if the drug is administered by a physician (or as prescribed by a physician)--(i) for use immediately before, at, or within 48 hours after the time of the administration of the anticancer chemotherapeutic agent; and (ii) as a full replacement for the anti-emetic therapy which would otherwise be administered intravenously."

The language of that law is specific. It stipulates that coverage would be extended to “an oral drug” in the singular, and does not specify that coverage be extended to an anti-emetic regimen that includes an oral drug. The language also specifies that the newly covered drug be prescribed “as a full replacement for the anti-emetic therapy which would otherwise be administered intravenously.” This language is clear. An oral anti-emetic would not be covered by Medicare if an intravenous anti-emetic therapy must also be administered to the patient to gain the required therapeutic effect.

Further, from our direct experience in working with Congress to craft that language, discussions surrounding the language revolved around replacing intravenous anti-emetic therapy with an oral version of that therapy. Both the intravenous and oral versions of the therapies that were discussed in relation to the BBA language had the same active ingredient. At present, all oral anti-emetics covered by Medicare Part B have the same active ingredient as an intravenous form of the product they replace.

That law was implemented by CMS in Program Memorandum AB-97-26 for intermediaries and carriers. That program memorandum specifically reiterates that the oral anti-emetic must be used as “full therapeutic replacements for intravenous anti-emetics that would have otherwise been administered at the time of the chemotherapy treatment.”

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (“MMA”) did not amend the oral anti-emetic coverage provisions in BBA but CMS’

implementation of a required demonstration project to extend coverage to selected oral replacement drugs suggests that a careful standard be maintained. Section 641 of MMA requires CMS to implement a replacement drug demonstration program that will cover certain self-injected or oral drugs not normally covered under Medicare Part B. To determine the criteria for defining a "replacement" drug under Section 641, CMS established an inter-agency panel of clinicians and considered public feedback. As a result of these efforts, to be covered as a "replacement" drug under the demonstration, a drug or biological must meet the following criteria:

- Drugs or biologicals must meet the statutory requirement of being a replacement by eliminating the concurrent need for a currently covered drug or biological for a currently covered indication;
- Coverage of the drug or biological in the demonstration is limited to FDA approved indications and, for any drug with an existing FDA approved indication, any additional indication if such additional indication is being reviewed by the FDA; and the requester has received documentation from the FDA that no filing issues remain;
- Drugs must be at least of equal efficacy to the covered drug for which it is a replacement;
- Use of the drug must represent an advantage in terms of access and/or convenience for patients compared to the currently covered drug; and
- Drugs are not eligible for coverage under this demonstration if the drug they are replacing is not commonly provided incident to a physician service (for example, anti-hypertensives, antibiotics, oral hypoglycemics, etc.).

These criteria are consistent with the language in the BBA relating to the coverage of oral anti-emetics.

APREPITANT DOES NOT MEET STATUTORY REQUIREMENTS FOR PART B MEDICARE COVERAGE

Aprepitant is approved by the FDA to be used only in conjunction with other approved drugs, each with an individual mechanism of action. It is not approved by the FDA for use as an individual drug, let alone full replacement for an existing intravenous drug. Neither is aprepitant included as a single agent in major, established anti-emetic guidelines.

The Dosage and Administration section of the prescribing information for aprepitant approved by the FDA states that aprepitant "is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT₃ antagonist." Further, the product information cites only clinical studies that included aprepitant, dexamethasone, and the full dose (32 mg IV) of ondansetron. Further, the prescribing information states that clinical "studies show that aprepitant augments the anti-emetic activity of the 5HT₃ receptor antagonist ondansetron and the corticosteroid dexamethasone."

Further, there are well established anti-emetic guidelines such as those created by Multinational Association for Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), and the National Comprehensive Care Network (NCCN) that clearly do not recommend single agent therapy with aprepitant for prevention of acute chemotherapy-induced nausea and vomiting. Additionally, for moderately

emetogenic chemotherapy, aprepitant is not included in the recommendations. 5HT₃ antagonists remain as the gold standard antiemetic, which is evident in these recommendations.

Currently, the guidelines recommend the following regimens:

	Highly Emetogenic	Moderately Emetogenic
MASCC	5HT ₃ + dex + aprepitant	5HT ₃ + dex
ASCO*	5HT ₃ + dex	5HT ₃ + dex
NCCN	5HT ₃ + dex + aprepitant ± lorazepam	5HT ₃ + dex ± lorazepam [†]

* ASCO guidelines were created prior to FDA-approval of aprepitant and have yet to be updated. ASCO also did not use the term “moderately emetogenic”; this recommendation is for highly emetogenic non-cisplatin. † aprepitant may be “considered in select patients”

A clinical study evaluating the antiemetic efficacy of aprepitant as a single agent for the prevention of CINV (highly or moderately emetogenic chemotherapy) has not been conducted, and there has been only one study that compared aprepitant + dexamethasone to a 5HT₃ antagonist + dexamethasone regimen:

Campos et al (*J Clin Oncol* 2001;19:1759-1767) conducted a multicenter, double-blind, parallel-group study in 351 cisplatin-naïve patients to evaluate the efficacy of aprepitant + dexamethasone vs. a 5HT₃ (granisetron) + dexamethasone for prevention of acute (day 1) and delayed (days 2-5) CINV associated with high-dose cisplatin. Merck & Co. funded and conducted this study prior to FDA approval, thus aprepitant is referred to as MK-869.

This study utilized higher doses (acute-400mg, delayed-300 mg) of aprepitant than the FDA-approved doses for both acute and delayed phases (125 mg, 80 mg, respectively).

Treatment Regimen		No Emesis (Day 1)	No Emesis (Days 2-5)
Day 1	Days 2-5		
granisetron + dex	Placebo	57%	29%
granisetron + dex + aprepitant	Aprepitant	80% [†]	63% [†]
aprepitant* + dex	Aprepitant	46%	51% [†]
aprepitant + dex	Aprepitant	43%	57% [†]

* Aprepitant was also given on the evening (day -1) before chemotherapy; † *P* < 0.01 vs. granisetron + dex

Although granisetron + dexamethasone was not statistically superior to aprepitant + dexamethasone, it “yielded a numerically superior control of acute emesis compared with the groups that received dual therapy with MK-869 [aprepitant] + dexamethasone (57%

vs. 46% and 43%)". Only the 3-drug regimen (granisetron + dex + aprepitant) was statistically superior to granisetron + dexamethasone. Aprepitant-containing regimens were statistically superior to granisetron + dex for the prevention of emesis in the delayed phase (days 2-5). Campose et al concluded that the "combination of the 5HT₃ antagonist + dexamethasone was numerically superior to MK-869 [aprepitant] + dexamethasone in reducing acute emesis. Confirming and extending previous findings, the triple combination of a 5HT₃ antagonist, MK-869 [aprepitant], and dexamethasone provided the best control of acute emesis."

Finally we wish to note that there has been some preliminary research, as described in an abstract presented at a recent ASCO meeting that might suggest that aprepitant could have a therapeutic effect when prescribed with an oral 5HT₃ agent. That study has not been published in any peer reviewed journal. Neither has this use of aprepitant been incorporated in any compendia or generally accepted guidelines for the treatment of chemotherapy induced nausea and vomiting. If these data are validated by additional, peer reviewed research, it is our view that this product would still not qualify for Part B coverage because the law refers to coverage of oral drug in the singular, and not a multi-product drug regimen.

For all of the above reasons, aprepitant does not meet the requirement of the BBA, which states, as noted above, "---an oral drug...as a full replacement for the anti-emetic therapy which would otherwise be administered intravenously."

APREPITANT DOES NOT REPLACE AN INTRAVENOUS OR INJECTABLE FORM OF NEUROKININ 1 ANTAGONISTS.

As mentioned above, discussions surrounding the crafting of the BBA language revolved around the full replacement of an intravenous formulation of anti-emetic therapy with an oral version of the therapy with the same active ingredient.

Aprepitant is the first of its kind neurokinin 1 antagonist ("NK1") for use as an anti-emetic. There are no intravenous or injectable forms of NK1 anti-emetics approved by the FDA. The Medicare statute requires among other things that Medicare can cover oral anti-emetics "as a full replacement for the anti-emetic therapy which would otherwise be administered intravenously." 42 U.S.C. sec.1395x(s)(2)(T). Aprepitant cannot serve as a "full replacement" because there is no intravenous NK1 that it would replace.

All other Medicare covered oral anti-emetics had intravenous precedents of the same drug. That policy gave Medicare patients assurance of the safety and effectiveness of the oral form as a "full replacement." CMS would be contravening its past practice to extend coverage to aprepitant, which has no intravenous formulation.

APREPITANT DOES NOT NEED TO BE COVERED NOW BY MEDICARE UNDER PART B

There are already several replacement drugs covered and available to Medicare beneficiaries. It is not clear if extending coverage for aprepitant in the coming year will significantly improve patient access compared to coverage that will be available under the drug discount program now available and under Part D. It would appear that Medicare can effectively advance patient access by utilizing existing authorities, rather than expending resources in the coverage process.

CONCLUSION

As indicated above, given existing law, aprepitant should not be covered under Medicare Part B because it is not used as a single drug to be a full replacement for an intravenous therapy. GlaxoSmithKline does believe that all appropriate cancer therapies, including supportive care therapies should be available without restriction under the new Medicare Part D benefit. Even if the law as defined in the 1997 BBA was not clear with regard to Part B coverage, it would be duplicative and possibly unnecessary for CMS to proceed with a full coverage analysis and determination now, recognizing that this product should qualify for coverage soon under the new Part D drug coverage benefit. Moreover, when so covered, Medicare may likely realize the cost savings that Congress intended when it created the special authority to cover anti-emetics.

We hope that these comments will be of assistance as CMS continues to evaluate this issue.

Commenter: Gralla, Richard J. MD

Organization: Multinational Association for Supportive Care in
Cancer

Date: August 5, 2004

Comment:

I am writing regarding the consideration of CMS to cover aprepitant (Emend«) for patients receiving highly emetogenic chemotherapy. As a physician who has focused for over 20 years on research and treatment associated with chemotherapy-induced emesis, I am certain that the evidence supports the importance of this agent in appropriate patients with cancer.

Large, well-powered and well-conducted studies clearly indicate that this first agent of its type, a neurokinin-1 (NK1) antagonist (blocking the effect of substance P), is a major step forward in cancer care. It is the first time in over a decade that we have had a new agent or class introduced that makes a substantial difference in reducing this most feared side effect of chemotherapy. Both the Hesketh (Journal of Clinical Oncology 2003) and the Poli-Bigelli (Cancer 2003) studies, including over 1000 patients, demonstrate a marked advantage for patients randomly assigned to receive this oral agent, aprepitant, added to the former standard antiemetic regimens.

As you are aware, combination antiemetic regimens have been indicated in patients receiving highly emetic chemotherapy for more than 15 years. This new combination of aprepitant plus a serotonin (5-HT₃ receptor) antagonist plus a corticosteroid establishes a new oral regimen that is a full and complete replacement for earlier regimens. Aprepitant is the only agent approved by the FDA for both acute and delayed emesis in patients receiving highly emetogenic chemotherapy, and has been so endorsed by the only two guideline groups (NCCN and MASCC) that have established new guidelines since the approval of this agent in 2003.

Of particular importance concerning the guidelines, is that fact that the serotonin antagonists are no longer recommended for delayed emesis in this group of patients in the latest guidelines. For those of us who consider that following evidence based recommendations can result in significant benefits in patient care, having CMS coverage consistent with guidelines and evidence will have a major impact on practice patterns in the community.

The new, all oral aprepitant-based combination regimen for patients receiving highly emetogenic chemotherapy is a major step forward in cancer care. Having coverage for this markedly effective regimen will be a great step forward for many patients undergoing treatment for advanced malignancy.

If I can add additional information, or assist you or your staff in any way, please do not hesitate to contact me. All of us in the supportive care oncology community appreciate the thoughtful and important work being conducted at CMS.

Commenter: Horgan, Kevin M.D. and Von Dohren, Denise

Organization: Merck

Date: August 4, 2004

Comment:

(See next page)

August 4, 2004

Steve Phurrough. M.D.
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Department of Health and Human Services
7500 Security Blvd.
Baltimore, MD 21244



Re: Aprepitant for Chemotherapy-Induced Emesis (CAG-00248N)

Dear Dr. Phurrough:

This letter sets out the body of clinical evidence demonstrating that, when appropriately prescribed in accordance with the FDA approved label and antiemetic consensus guidelines, an antiemetic regimen including aprepitant is a full replacement of an IV antiemetic regimen for patients receiving highly emetogenic chemotherapy. Accordingly, we respectfully request that CMS establish a national coverage policy that provides Medicare beneficiaries access to this unique therapy that effectively treats an important unmet medical need.

Prevalence of CINV

Severe nausea and vomiting are two of the primary side effects of Medicare beneficiaries who undergo chemotherapy for cancer. These symptoms can be severely debilitating, can lead to patients' refusing further courses of chemotherapy or can impose serious limitations on their lifestyle, and can result in hospitalization which may have been prevented.

There are three types of emesis: a) acute which occurs within 24 hours of the initiation of chemotherapy, b) delayed which occurs more than 24 hours after chemotherapy and c) anticipatory (a conditioned response resulting from prior poor control of either acute or delayed emesis). Although therapies such as 5-HT₃ antagonists have substantively contributed to preventing emesis, several clinical studies and oncologists' practical experiences show that there is still a marked need for prevention of chemotherapy induced emesis, throughout both the acute and delayed phases.

NK1 Antagonist

Aprepitant is the first and only neurokinin-1 (NK₁) antagonist approved by the FDA. Aprepitant selectively inhibits NK₁ receptors in the brain that control emesis while treatments such as ondansetron (Zofran®) and palonosetron (Aloxi®) are 5-HT₃ antagonists that primarily inhibit receptors in the gut. The effectiveness and mechanism of action of NK₁ antagonists against both acute and delayed emesis separates it from the serotonin (or 5-HT₃) antagonists, which

are not indicated for delayed emesis caused by highly emetogenic chemotherapy (this now represents the most difficult emetic problem).

Clinical Evidence on Aprepitant

In March of 2003, the FDA approved aprepitant. It is the first and only antiemetic drug with its specific, unique mechanism of action and the first oral drug ever approved for use in combination with antiemetics for the prevention of acute and delayed emesis associated with highly emetic chemotherapy. As an innovative drug and the first in its therapeutic class to fill an important unmet clinical need, aprepitant was one of only eight new molecular entities granted priority review by FDA in 2003. Priority review is granted only to drugs or biologics that offer a "significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease."

The efficacy and antiemetic activity of the aprepitant regimen were principally demonstrated in two large multicenter, randomized, double-blind clinical studies in comparison to the existing standard antiemetic regimen of a 5-HT₃ antagonist (ondansetron) and a corticosteroid (dexamethasone). The two trials found that patients receiving the antiemetic regimen with aprepitant showed a marked and highly significant improvement in the prevention of emesis (an absolute 20% improvement over standard anti-emetic therapy, $p < 0.001$). The trials also demonstrated that the percentage of patients who remained emesis-free over five days following initiation of chemotherapy was significantly higher for those receiving the aprepitant regimen than for those receiving standard therapy ($p < 0.001$).

In addition, an analysis of these two Phase III trials showed that treatment with aprepitant in combination with a 5-HT₃ receptor antagonist and a corticosteroid significantly improved emetic prevention in both genders and was generally well tolerated compared with a 5-HT₃ receptor antagonist and a corticosteroid alone.

The FDA approved use of aprepitant with an anti-emetic regimen including a 5-HT₃ antagonist and a corticosteroid is for the day of chemotherapy. The regimen includes a 5-HT₃ antagonist on the day of chemotherapy to prevent acute emesis or nausea and vomiting that occur within 24 hours of highly emetogenic chemotherapy. In fact, the results of the clinical trials demonstrate that a regimen including aprepitant, a 5-HT₃ antagonist and a corticosteroid reduced the remaining risk from highly emetogenic chemotherapy by over 50% relative to a regimen of a 5-HT₃ antagonist and corticosteroid alone. To achieve complete prevention of acute and delayed emesis for patients undergoing highly emetogenic chemotherapy, the FDA approved a three dose administration of aprepitant. It should be emphasized that aprepitant, when used with other antiemetics, can not achieve its unique benefit – prevention of acute and delayed emesis in patients undergoing highly emetogenic chemotherapy – if aprepitant is not administered in accordance with the approved FDA label – i.e., 125mg loading dose on the day of chemotherapy with a 5-HT₃ antagonist and a

corticosteroid and an 80mg dose once a day with corticosteroid within 48 hours after chemotherapy.

Antiemetic Guidelines

The National Comprehensive Cancer Network (NCCN) Antiemesis Clinical Practice Guidelines¹ panel issued a new set of recommendations establishing aprepitant as the lead agent in the new standard of care at their annual meeting in March, 2004. Specifically, NCCN recommended aprepitant as a first-line antiemetic therapy to prevent chemotherapy-induced emesis for patients undergoing highly emetogenic chemotherapy.

In March 2004, the Multinational Association of Supportive Care in Cancer (MASCC) also revised and issued antiemetic guidelines on the website². These guidelines are a statement of consensus regarding evidence-based antiemetic treatment approaches by nine committees with representatives from nine international oncology groups³. All nine international consensus committees that have reviewed aprepitant have endorsed aprepitant as a standard of care for acute and delayed emesis for patients undergoing highly emetogenic chemotherapy.

Coverage

Aprepitant would be covered in accordance with the FDA label and evidence based antiemetic guidelines. Aprepitant is approved for use in combination with other antiemetic agents and is indicated for the prevention of acute and delayed nausea and vomiting associated with the initial and repeat courses of highly emetogenic cancer chemotherapy.

Highly emetogenic chemotherapy includes, but is not limited to, patients receiving chemotherapies where there is a greater than 90% risk of emesis. The chemotherapies that, based on the evidence available as of March 2004, are considered highly emetic are included in the consensus guidelines and referenced on the MASCC website⁴. In addition, coverage would include combinations of chemotherapy that result in high emetogeneity. As you know, it will be necessary for coverage to be updated as emetogeneity guidelines are changed and new chemotherapeutic agents enter the marketplace.

Consistent with the approved FDA label for aprepitant and the consensus guidelines, the dosing regimen for aprepitant is 125 mg orally 1 hour prior to

¹ Website www.NCCN.com (website accessed April 2, 2004)

² Website www.MASCC.org (website accessed June 14, 2004)

³ See Table 1 for professional oncology organizations represented.

⁴ Available at http://www.mascc.org/files/MASCC_guide-slides060804-1st_ed.pps

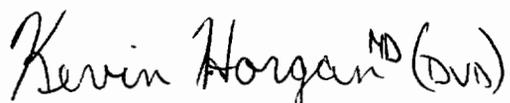
chemotherapy treatment in combination with a 5-HT₃ antagonist and a corticosteroid on Day 1 and 80 mg once daily within 48 hours after the administration of highly emetogenic chemotherapy (see Table 2).

Conclusion

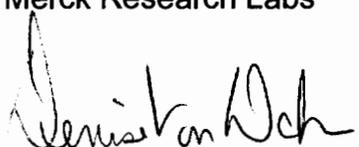
We respectfully request that CMS consider, consistent with the FDA label for aprepitant and national guidelines, providing Medicare beneficiaries access to an anti-emetic regimen including aprepitant for patients receiving highly emetogenic chemotherapy when this regimen fully replaces the intravenous anti-emetic regimen. Patients have continuing need for better prevention of chemotherapy induced emesis and new therapies that effectively treat this important unmet patient need.

For your reference, please find the enclosed prescribing information for Emend®

Sincerely,



Kevin Horgan, M.D.
Senior Director
Merck Research Labs



Denise Von Dohren
Senior Manager
Reimbursement Planning

Table 1

International:	MASCC
North America:	
- U.S.	ASCO, ONS, NCCN
- Canada	CCO
Europe:	ESMO, EONS
Africa:	SASMO
Australia:	COSA

Table 2

Regimen	Day 1 (The day of Chemotherapy)	Day 2	Day 3
Aprepitant	125 mg	80 mg	80 mg
Dexamethasone	12 mg	8mg	8 mg
Serotonin (5-HT3) Antagonist	Ond: 8 – 32 mg Gran: 1 – 2 mg Dolas: 100 mg Palo: 0.25 mg	---	---

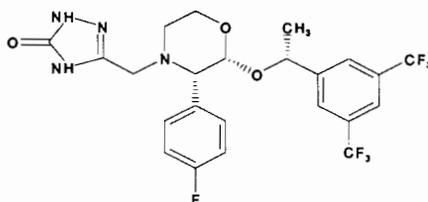
Note: All agents are given only once daily.

EMEND®
(aprepitant)
CAPSULES

DESCRIPTION

EMEND® (aprepitant) is a substance P/neurokinin 1 (NK₁) receptor antagonist, chemically described as 5-[[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is C₂₃H₂₁F₇N₄O₃, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

Each capsule of EMEND for oral administration contains either 80 mg or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin and titanium dioxide. The 125-mg capsule also contains red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK₁) receptors. Aprepitant has little or no affinity for serotonin (5-HT₃), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV).

Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK₁ receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT₃-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

Pharmacokinetics

Absorption

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}). Oral

administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state.

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} was approximately 19.6 mcg•hr/mL and 21.2 mcg•hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1.6 mcg/mL and 1.4 mcg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

Distribution

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state ($V_{d_{ss}}$) is approximately 70 L in humans.

Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans (see CLINICAL PHARMACOLOGY, *Mechanism of Action*).

Metabolism

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [¹⁴C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

Following administration of a single IV 100-mg dose of [¹⁴C]-aprepitant prodrug to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces. A study was not conducted with radiolabeled capsule formulation. The results after oral administration may differ.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent plasma clearance of aprepitant ranged from approximately 62 to 90 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Special Populations

Gender

Following oral administration of a single 125-mg dose of EMEND, no difference in AUC_{0-24hr} was observed between males and females. The C_{max} for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary based on gender.

Geriatric

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 through 5, the AUC_{0-24hr} of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥65 years) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary in elderly patients.

Pediatric

The pharmacokinetics of EMEND have not been evaluated in patients below 18 years of age.

Race

Following oral administration of a single 125-mg dose of EMEND, the AUC_{0-24hr} is approximately 25% and 29% higher in Hispanics as compared with Whites and Blacks, respectively. The C_{max} is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in AUC_{0-24hr} or C_{max} between Whites and Blacks. No dosage adjustment for EMEND is necessary based on race.

Hepatic Insufficiency

EMEND was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the AUC_{0-24hr} of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the AUC_{0-24hr} of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC_{0-24hr} are not considered clinically meaningful; therefore, no dosage adjustment for EMEND is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9) (see PRECAUTIONS).

Renal Insufficiency

A single 240-mg dose of EMEND was administered to patients with severe renal insufficiency (CrCl<30 mL/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal insufficiency, the AUC_{0-∞} of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the AUC_{0-∞} of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No dosage adjustment for EMEND is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.

Clinical Studies

Oral administration of EMEND in combination with ondansetron and dexamethasone (aprepitant regimen) has been shown to prevent acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy including high-dose cisplatin.

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen (see table below) was compared with standard therapy in patients receiving a chemotherapy regimen that included cisplatin >50 mg/m² (mean cisplatin dose = 80.2 mg/m²). Of the 550 patients who were randomized to receive the aprepitant regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The aprepitant-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. 170 patients were 65 years or older, with 29 patients being 75 years or older.

Patients (N = 1105) were randomized to either the aprepitant regimen (N = 550) or standard therapy (N = 555). The treatment regimens are defined in the table below.

Treatment Regimens

Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg IV	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 32 mg IV	Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

During these studies 95% of the patients in the aprepitant group received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the number of aprepitant patients exposed follows: etoposide (106),

fluorouracil (100), gemcitabine (89), vinorelbine (82), paclitaxel (52), cyclophosphamide (50), doxorubicin (38), docetaxel (11).

The antiemetic activity of EMEND was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following endpoints:

Primary endpoint:

- complete response (defined as no emetic episodes and no use of rescue therapy)

Other prespecified (secondary and exploratory) endpoints:

- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)

A summary of the key study results from each individual study analysis is shown in Table 1 and in Table 2.

Table 1

Percent of Patients Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N= 260) [†] %	Standard Therapy (N= 261) [†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall [‡]	73	52	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase [§]	89	78	<0.001
Delayed phase [¶]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	0.005
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	>0.050
Delayed phase	51	48	>0.050
No Significant Nausea			
Overall	73	66	>0.050
Delayed phase	75	69	>0.050

[†]N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

[‡]Overall: 0 to 120 hours post-cisplatin treatment.

[§]Acute phase: 0 to 24 hours post-cisplatin treatment.

[¶]Delayed phase: 25 to 120 hours post-cisplatin treatment.

Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

Table 1 includes nominal p-values not adjusted for multiplicity.

Table 2
Percent of Patients Responding by Treatment Group and Phase for Study 2 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N= 261) [†] %	Standard Therapy (N= 263) [†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall [‡]	63	43	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase [§]	83	68	<0.001
Delayed phase [¶]	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	0.021
Delayed phase	53	40	0.004
No Significant Nausea			
Overall	71	64	>0.050
Delayed phase	73	65	>0.050

[†]N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

[‡]Overall: 0 to 120 hours post-cisplatin treatment.

[§]Acute phase: 0 to 24 hours post-cisplatin treatment.

[¶]Delayed phase: 25 to 120 hours post-cisplatin treatment.

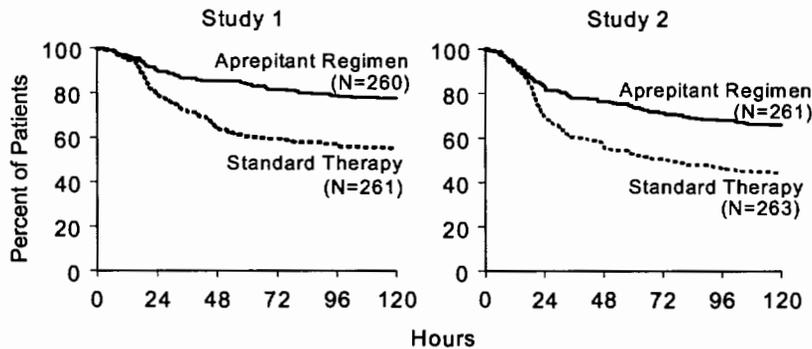
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

Table 2 includes nominal p-values not adjusted for multiplicity.

In both studies, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favor of the aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 1.

Figure 1: Percent of Patients Who Remain Emesis Free Over Time – Cycle 1

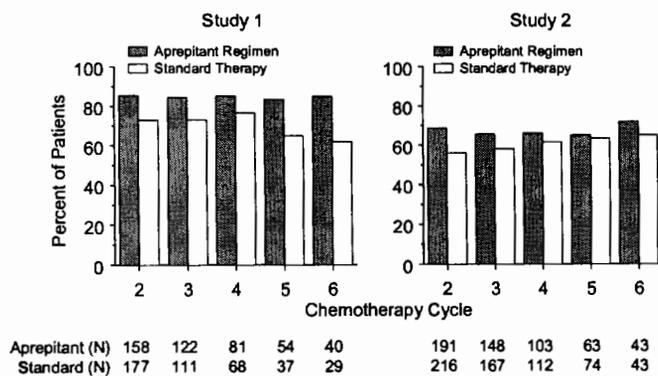


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase III studies using the Functional Living Index–Emesis (FLIE), a validated nausea- and vomiting-specific patient-reported outcome measure. Minimal or no impact of nausea and vomiting on patients' daily lives is defined as a FLIE total score >108. In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

Multiple-Cycle Extension: In the same 2 clinical studies, patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with no emesis and no significant nausea by treatment group at each cycle is depicted in Figure 2. Antiemetic effectiveness for the patients receiving the aprepitant regimen is maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Figure 2: Proportion of Patients With No Emesis and No Significant Nausea by Treatment Group and Cycle



INDICATIONS AND USAGE

EMEND, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

EMEND is a moderate CYP3A4 inhibitor. EMEND should not be used concurrently with pimozone, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see PRECAUTIONS, *Drug Interactions*).

EMEND is contraindicated in patients who are hypersensitive to any component of the product.

PRECAUTIONS

General

EMEND should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see PRECAUTIONS, *Drug Interactions*).

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, EMEND was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates docetaxel, vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied (see PRECAUTIONS, *Drug Interactions*).

Chronic continuous use of EMEND for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Coadministration of EMEND with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle (see PRECAUTIONS, *Drug Interactions*).

The efficacy of oral contraceptives during administration of EMEND may be reduced. Although effects on contraception with a 3-day regimen of EMEND given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used (see PRECAUTIONS, *Drug Interactions*).

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9). Therefore, caution should be exercised when EMEND is administered in these patients (see CLINICAL PHARMACOLOGY, *Special Populations, Hepatic Insufficiency* and DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with EMEND and to reread it each time the prescription is renewed.

Patients should be instructed to take EMEND only as prescribed. Patients should be advised to take their first dose (125 mg) of EMEND 1 hour prior to chemotherapy treatment.

EMEND may interact with some drugs including chemotherapy; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.

Administration of EMEND may reduce the efficacy of oral contraceptives. Patients should be advised to use alternative or back-up methods of contraception.

Drug Interactions

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Effect of aprepitant on the pharmacokinetics of other agents

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of EMEND with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

EMEND is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of EMEND with digoxin in a clinical drug interaction study.

5-HT₃ antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron or granisetron. No clinical or drug interaction study was conducted with dolasetron.

Corticosteroids:

Dexamethasone: EMEND, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and EMEND when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, by 2.2-fold on Days 1 and 5. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND, to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).

Methylprednisolone: EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.34-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The IV methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND.

Chemotherapeutic agents: See PRECAUTIONS, *General*.

Warfarin: A single 125-mg dose of EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of EMEND on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with EMEND. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.

Tolbutamide: EMEND, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15.

Oral contraceptives: Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%; therefore, the efficacy of oral contraceptives during administration of EMEND may be reduced. Although a 3-

day regimen of EMEND given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used.

Midazolam: EMEND increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with EMEND.

In another study with intravenous administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. EMEND increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of EMEND on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

Effect of other agents on the pharmacokinetics of aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of EMEND with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of EMEND.

Ketoconazole: When a single 125-mg dose of EMEND was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of EMEND with strong CYP3A4 inhibitors should be approached cautiously.

Rifampin: When a single 375-mg dose of EMEND was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold.

Coadministration of EMEND with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of EMEND.

Additional interactions

Diltiazem: In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate or blood pressure beyond those changes induced by diltiazem alone.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Three 2-year carcinogenicity studies of aprepitant (two in Sprague-Dawley rats and one in CD-1 mice) were conducted with aprepitant. Dose selection for the studies was based on saturation of absorption in both species. In the rat carcinogenicity studies, animals were treated with oral doses of 0.05, 0.25, 1, 5, 25, 125 mg/kg twice daily. The highest dose tested produced a systemic exposure to aprepitant (plasma AUC_{0-24hr}) of 0.4 to 1.4 times the human exposure (AUC_{0-24hr} =

19.6 mcg•hr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 125 mg/kg twice per day produced thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced increased incidences of hepatocellular adenoma at 25 and 125 mg/kg twice daily, and thyroid follicular adenoma at the 125 mg/kg twice daily dose. In the mouse carcinogenicity study, animals were treated with oral doses of 2.5, 25, 125, and 500 mg/kg/day. The highest tested dose produced a systemic exposure of about 2.2 to 2.7 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas in male mice of 125 and 500 mg/kg/day groups.

Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

Pregnancy. Teratogenic Effects: Category B. Teratology studies have been performed in rats at oral doses up to 1000 mg/kg twice daily (plasma AUC_{0-24hr} of 31.3 mcg•hr/mL, about 1.6 times the human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma AUC_{0-24hr} of 26.9 mcg•hr/mL, about 1.4 times the human exposure at the recommended dose) and have revealed no evidence of impaired fertility or harm to the fetus 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, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Aprepitant is excreted in the milk of rats. It is not known whether this drug 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.

Pediatric Use

Safety and effectiveness of EMEND in pediatric patients have not been established.

Geriatric Use

In 2 well-controlled clinical studies, of the total number of patients (N=544) treated with EMEND, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

ADVERSE REACTIONS

The overall safety of aprepitant was evaluated in approximately 3300 individuals.

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. EMEND was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, clinical adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 68% of patients treated with standard therapy. Table 3 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3% during Cycle 1 of the 2 combined Phase III studies.

Table 3
Percent of Patients With Clinical Adverse Experiences (Incidence ≥3%)
In CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
Body as a Whole/ Site 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	4.0	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
Eyes, Ears, Nose, and Throat		
Tinnitus	3.7	3.8
Hemic and Lymphatic System		
Neutropenia	3.1	2.9
Metabolism and 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

The following additional clinical adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen:

Body as a whole: diaphoresis, edema, flushing, malaise, malignant neoplasm, pelvic pain, septic shock, upper respiratory infection.

Cardiovascular system: deep venous thrombosis, hypertension, hypotension, myocardial infarction, pulmonary embolism, tachycardia.

Digestive system: acid reflux, deglutition disorder, dysgeusia, dyspepsia, dysphagia, flatulence, obstipation, salivation increased, taste disturbance.

Endocrine system: diabetes mellitus.

Eyes, ears, nose, and throat: nasal secretion, pharyngitis, vocal disturbance.

Hemic and lymphatic system: anemia, febrile neutropenia, thrombocytopenia.

Metabolism and nutrition: appetite decreased, hypokalemia, weight loss.

Musculoskeletal system: muscular weakness, musculoskeletal pain, myalgia.

Nervous system: peripheral neuropathy, sensory neuropathy.

Psychiatric disorder: anxiety disorder, confusion, depression.

Respiratory system: cough, dyspnea, lower respiratory infection, non-small cell lung carcinoma, pneumonitis, respiratory insufficiency.

Skin and skin appendages: alopecia, rash.

Urogenital system: dysuria, renal insufficiency.

Laboratory Adverse Experiences

Table 4 shows the percent of patients with laboratory adverse experiences reported at an incidence $\geq 3\%$ during Cycle 1 of the 2 combined Phase III studies.

Table 4

Percent of Patients With Laboratory Adverse Experiences (Incidence $\geq 3\%$) in CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
ALT Increased	6.0	4.3
AST Increased	3.0	1.3
Blood Urea Nitrogen Increased	4.7	3.5
Serum Creatinine Increased	3.7	4.3
Proteinuria	6.8	5.3

The following additional laboratory adverse experiences (incidence $>0.5\%$ and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen: alkaline phosphatase increased, hyperglycemia, hyponatremia, leukocytes increased, erythrocyturia, leukocyturia.

The adverse experiences of increased AST and ALT were generally mild and transient.

The adverse experience profile in the Multiple-Cycle extension for up to 6 cycles of chemotherapy was generally similar to that observed in Cycle 1.

In addition, isolated cases of serious adverse experiences, regardless of causality, of bradycardia, disorientation, and perforating duodenal ulcer were reported in CINV clinical studies.

Stevens-Johnson syndrome was reported in a patient receiving aprepitant with cancer chemotherapy in another CINV study. Angioedema and urticaria were reported in a patient receiving aprepitant in a non-CINV study.

OVERDOSAGE

No specific information is available on the treatment of overdosage with EMEND. Single doses up to 600 mg of aprepitant were generally well tolerated in healthy subjects. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375-mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated.

Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective.

Aprepitant cannot be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT₃ antagonist. The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. EMEND has not been studied for the treatment of established nausea and vomiting.

In clinical studies, the following regimen was used:

	Day 1	Day 2	Day 3	Day 4
EMEND*	125 mg	80 mg	80 mg	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally

EMEND®
(aprepitant)

9565001

Ondansetron†	32 mg IV	none	none	none
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*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.

**Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone was chosen to account for drug interactions.

†Ondansetron was administered 30 minutes prior to chemotherapy treatment on Day 1.

Chronic continuous administration is not recommended (see PRECAUTIONS).

See PRECAUTIONS, *Drug Interactions* for additional information on dose adjustment for corticosteroids when coadministered with EMEND.

Refer to the full prescribing information for coadministered antiemetic agents.

EMEND may be taken with or without food.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary for patients with renal insufficiency or for patients with end stage renal disease undergoing hemodialysis.

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).

HOW SUPPLIED

No. 3854 — 80 mg capsules: White, opaque, hard gelatin capsule with “461” and “80 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0461-30 bottles of 30 (with desiccant)

NDC 0006-0461-05 unit-dose packages of 5.

No. 3855 — 125 mg capsules: Opaque, hard gelatin capsule with white body and pink cap with “462” and “125 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0462-30 bottles of 30 (with desiccant)

NDC 0006-0462-05 unit-dose packages of 5.

No. 3862 — Unit-of-use tri-fold pack containing one 125 mg capsule and two 80 mg capsules.

NDC 0006-3862-03.

Storage

Bottles: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. The desiccant should remain in the original bottle.

Blisters: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Rx only

 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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