

Drug Name: Aprepitant (Emend®)

Manufacturer: Merck & Co., Inc.

Pharmacology: Aprepitant (previously known as MK-0839 and L-754030) is a new molecular entity that is the first in a new therapeutic class, the nonpeptide, selective NK₁-receptor antagonist. In preclinical studies it has been found that substance P is the preferred agonist for the NK₁-receptor. Administration of substance P into the region of the nucleus tractus solitarius produces vomiting in animal models. NK₁-receptors are found in brain regions that are critical for the regulation of the vomiting reflex in the brain stem nuclei of the dorsal vagal complex. Aprepitant crosses the blood brain barrier and occupies the brain NK₁ receptors to exert its antiemetic effect. It has little or no affinity for serotonin (5-HT₃), dopamine, and corticosteroid receptors.

Pharmacokinetics: The oral bioavailability of aprepitant is approximately 60 to 65%. Food does not affect its absorption. Aprepitant is greater than 95% bound to plasma proteins. It undergoes extensive metabolism primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. There are seven metabolites of aprepitant, which are only weakly active. Aprepitant is eliminated primarily by metabolism. It is not renally excreted. The elimination half-life of aprepitant ranged from approximately 9 to 13 hours.

Approved Indication: In combination with other antiemetic agents 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.

Contraindications:

- Patients who are hypersensitive to any component of the product
- Patients who are taking pimozide, terfenadine, astemizole or cisapride

Drug Interactions: Aprepitant has a complex metabolic pathway. It is a substrate, a moderate inhibitor, as well as an inducer of CYP3A4. In addition, it is also an inducer of CYP2C9.

When aprepitant is administered for more than 28 days, it is an inducer of CYP3A4 and can autoinduce its own metabolism. When it is given by its approved 3-day regimen, it is a CYP3A4 inhibitor. Aprepitant can increase the area under the curve of corticosteroids by 1.3 to 2.3 folds, resulting to the need for dose reduction of corticosteroids during Phase 2 and 3 clinical trials.

Aprepitant may also reduce the effectiveness of oral contraceptives. Women of childbearing years should use another form of birth control when using aprepitant. Patients being treated with warfarin will need to have their INR tested after the completion of their 3-day regimen that includes aprepitant with each chemotherapy cycle to see if warfarin's dose needs to be changed.

The potential for serious drug-drug interactions of aprepitant with chemotherapeutic agents has not been thoroughly evaluated. During Phase 3 studies, approximately 95% of subjects received a concomitant chemotherapeutic agent in addition to cisplatin. However, there is only limited safety data for most 3A4 metabolized oncologic agents. Currently, pharmacokinetics and drug-drug interaction studies of aprepitant with other chemotherapeutic agents are ongoing in the post-marketing phase.

Clinical Studies:

Authors	Study Design	Treatment		Efficacy	Safety
Poli-Bigelli S 2003 (Study 054 reviewed by FDA)	MC, DB, RCT Phase 3 569 cisplatin- naïve patients First cycle of cisplatin-based ($\geq 70\text{mg/m}^2$) chemotherapy	Group 1	Group 2	523 evaluable patients <i>Primary endpoint:</i> No emesis & no rescue meds on days 1-5 Group 1: 62.7% Group 2: 43.3% ($p < 0.001$) <i>Secondary endpoints:</i> a) No emesis & no rescue meds on day 1 Group 1: 82.8% Group 2: 68.4% ($p < 0.01$) b) No emesis & no rescue meds on day 2-5 Group 1: 67.7% Group 2: 46.8% ($p < 0.01$) c) No nausea on days 1-5 Group 1: 48.8% Group 2: 28.8% ($p = 0.021$)	568 evaluable patients Overall AE was similar between treatment groups
		Day 1 APR 125mg PO DEX 12mg PO OND 32mg IV	Day 1 PLB DEX 20mg PO OND 32mg IV		
Unpublished (Study 052 reviewed by FDA)	MC, DB, RCT Phase 3 534 cisplatin- naïve patients First cycle of cisplatin-based ($\geq 70\text{mg/m}^2$) chemotherapy	Day 2-4 APR 80mg PO QD (days 2 & 3 only) DEX 8mg PO QD (days 2-4)	Day 2-4 PLB DEX 8mg PO BID (days 2-4)	520 evaluable patients <i>Primary endpoint:</i> No emesis & no rescue meds on days 1-5 Group 1: 72.7% Group 2: 52.3% ($p < 0.001$) <i>Secondary endpoints:</i> a) No emesis & no rescue meds on day 1 Group 1: 89.2% Group 2: 78.1% ($p < 0.001$) b) No emesis & no rescue meds on day 2-5 Group 1: 75.4% Group 2: 55.8% ($p < 0.001$) c) No nausea on days 1-5 Group 1: 47.5% Group 2: 44.2% ($p = 0.48$)	526 evaluable patients Overall AE was similar between treatment groups
		Day 1 APR 125mg PO DEX 12mg PO OND 32mg IV	Day 1 PLB DEX 20mg PO OND 32mg IV		

Authors	Study Design	Treatment	Efficacy	Safety
Chawla SP 2003	MC, DB, RCT 583 cisplatin-naïve patients First cycle of cisplatin-based ($\geq 70\text{mg/m}^2$) chemotherapy	All received OND 32mg IV/DEX 20mg PO on Day 1 and DEX 8mg PO QD Days 2-5 plus one of the following: 1. APR 375mg Day 1 and 250mg Days 2-5 2. APR 125mg Day 1 and 80mg Days 2-5 3. PLB Days 1-5 Due to pharmacokinetic interaction between APR 375/250-mg regimen and DEX, this study arm was discontinued and replaced with APR 40/25-mg dose regimen	377 evaluable patients <i>Primary endpoint:</i> No emesis & no rescue meds on days 1-5 1. 125/80-mg: 71% 2. 40/25-mg: 58.8% 3. PLB: 43.7%* (*p<0.05 compared to 125/80-mg or 40/25-mg) <i>Secondary endpoints:</i> a) No emesis & no rescue meds on days 1 1. 125/80-mg: 83.2%* 2. 40/25-mg: 75.6% 3. PLB: 71.4% (*p=0.014 vs. PLB) b) No emesis & no rescue meds on days 2-5 1. 125/80-mg: 72.7% 2. 40/25-mg: 63.9% 3. PLB: 45.2%* (*p<0.01 compared to 125/80-mg or 40/25-mg) c) No nausea on days 1-5 1. 125/80-mg: 52.7% 2. 40/25-mg: 48% 3. PLB: 34.1%* (*p<0.05 compared to 125/80-mg or 40/25-mg)	580 evaluable patients APR 125/80-mg group had the highest rates of AE, drug-related AE, and discontinuations due to serious AE compared to the other two groups (p>0.05). Infection-related serious AE was more commonly reported in 125/80-mg group (13%) compare to PLB group (4.2%) (p-value not reported). Incidence of all other AEs was similar among treatment groups.
Navari RM 1999	MC, DB, Phase 2 159 cisplatin-naïve patients Single-dose of $\geq 70\text{mg/m}^2$ cisplatin	All received GRA 10mcg/kg IV/DEX 20mg PO on Day 1 plus one of the following: 1. L-754,030 400mg PO Day 1, 300mg PO QD Days 2-5 2. L-745,030 400mg PO Day 1, PLB Days 2-5 3. PLB Days 1-5	<i>Primary endpoint:</i> No emesis on days 2-5 1. 82% 2. 78% 3. 33%* (*p<0.001 compared to Group 1 or 2) <i>Secondary endpoint:</i> Self-assessment of nausea - visual analogue scale median score for overall and delayed phases Group 1 lower than PLB (p<0.003)	Overall AE was similar among treatment groups

Authors	Study Design	Treatment	Efficacy	Safety
Campos D 2001	MC, DB, RCT Phase 2 351 cisplatin-naïve patients First cycle of cisplatin-based ($\geq 70 \text{ mg/m}^2$) chemotherapy	All received DEX 20mg PO on Day 1 plus one of the following: 1. GRA 10mcg/kg IV Day 1, PLB Days 2-5 2. GRA 10mcg/kg/MK-839 400mg PO Day 1, MK-869 300mg PO QD Days 2-5 3. MK-839 400mg PO Day 1 and evening pre-cisplatin, MK-869 300mg PO QD Days 2-5 4. MK-839 400mg PO Day 1, MK-869 300mg PO QD Days 2-5	<i>Primary endpoint:</i> No emesis on days 2-5 1. 29% 2. 63%* 3. 51%* 4. 57%* (*p<0.01 compared to Group 1) <i>Secondary endpoint:</i> Self-assessment of nausea - visual analogue scale median score for overall and delayed phases Group 2 lower than Group 1 (p<0.05 on days 1-5; p=0.05 on days 2-5).	Overall AE was similar among treatment groups except diarrhea Incidence of diarrhea: 1. 17% 2. 16% 3. 40% 4. 36%
Cocquyt V 2001	MC, DB, RCT 53 cisplatin-naïve patients Single-dose of 50-100 mg/m ² cisplatin ?? first cycle of cisplatin	1. L-758,298** (60 or 100mg) IV x 1 2. OND 32mg IV x 1 Doses given 60min prior to cisplatin	<i>Primary endpoint:</i> No emesis in acute phase (initial 24h post cisplatin) 1. L-758,298: 37% 2. OND: 52% (p=0.28) <i>Secondary endpoints:</i> Self-assessment of nausea scores <u>Acute phase (day 1)</u> OND lower than L-758,298 (p=0.11) <u>Delayed phase (days 2-7)</u> L-758,298 lower than OND (p=0.15)	Overall AE was similar between treatment groups except diarrhea Incidence of diarrhea: 1. L-758,298: 60% 2. OND: 9%

Authors	Study Design	Treatment	Efficacy	Safety
Van Belle S 2002	MC, DB, RCT 177 cisplatin-naïve patients First cycle of cisplatin-based ($\geq 70\text{mg/m}^2$) chemotherapy	All received DEX 20mg IV on Day 1 plus one of the following: 1. L-758,298** 100mg IV Day 1, MK-869 300mg PO QD Days 2-5 2. L-758,298 100mg IV Day 1, PLB Days 2-5 3. OND 32mg IV Day 1, PLB Days 2-5	<i>Primary endpoints:</i> No emesis & no rescue meds <u>Acute phase (day 1)</u> 1. 44% 2. 36% 3. 83%* (*p<0.001 compared to Group 1 or 2) <u>Delayed phase (days 2-5)</u> 1. 59%* 2. 46% 3. 38% (*p<0.05 vs. Group 3) <i>Secondary endpoints:</i> Self-assessment of nausea scores <u>Acute phase (day 1)</u> Group 3 was lower than Group 1 and 2 (p<0.05) <u>Delayed phase (days 2-5)</u> Group 3 was lower than Group 1 and 2 (p>0.05)	Overall AE was similar among treatment groups except diarrhea Incidence of diarrhea: 1. 23% 2. 23% 3. 5%

RCT=randomized controlled trial, DB=double blind, MC=multicenter, APR=aprepitant, OND=ondansetron, GRA=granisetron, DEX=dexamethasone, PLB=placebo, AE=adverse event; **L-758-298 is water-soluble, prodrug of aprepitant.

Based on the two FDA reviewed Phase 3 clinical trials, complete protection from delayed emesis was achieved in 68% and 75% of patients treated with aprepitant regimen. The results of the no nausea endpoints were not as robust. Statistically significant improvement over standard therapy on the no nausea endpoint in overall phase was only found in one of the two studies. If total control, that is no emesis, no use of rescue medications, and no nausea during the overall, acute and delayed phases, is examined, aprepitant regimen did show an improvement over standard therapy for both studies; however, statistical significance was only found in one.

Adverse Events: In general, the incidences of clinical and laboratory adverse events were similar between aprepitant and active comparators in the Phase 2 and 3 clinical trials. The most common adverse event that occurred more frequently in the aprepitant group compared with the standard group in the Phase 3 studies are: asthenia/fatigue (17.8% and 11.8%), dizziness (6.6% and 4.4%), diarrhea (10.3% and 7.3%), cough (2.4% and 0.5%), and hiccups (10.8% and 5.6%).

There were more infection-related adverse events reported in the aprepitant group compared to the standard therapy group. Serious infection-related adverse events occurred in 3.7% of patients receiving aprepitant during Cycle 1, compared to 2.4% of patients in the standard therapy group. There were also more serious adverse events of hematologic toxicity associated with the aprepitant group than the standard therapy group. However, the significance of these differences is uncertain.

Dosage and Administration: Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT₃ antagonist. The recommended dose of aprepitant is 125mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80mg once daily in the morning on Days 2 and 3.

Aprepitant has not been studied for the treatment of established nausea and vomiting. Chronic continuous administration is not recommended per manufacturer. Aprepitant is available in 80mg and 125mg capsules.

Special Populations: No significant treatment-by-age interaction for aprepitant was noted in the Phase 3 clinical trials. Aprepitant is not approved for use in the pediatric population. The manufacturer is currently conducting post-marketing trials to evaluate the efficacy and safety of aprepitant in the pediatric population.

Pregnancy was part of the exclusion criteria for all the studies. Aprepitant is currently classified as Pregnancy Category B.

Cost: A 3-day course of 80mg/day is \$303.75 AWP.

Summary: Aprepitant is the first FDA approved agent for the prevention of delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. It offers a novel mechanism of action for prevention of chemotherapy-induced emesis and nausea. Before aprepitant was available, metoclopramide or a 5-HT₃ antagonist in combination with dexamethasone or dexamethasone monotherapy has been recommended for cisplatin-induced delayed nausea and vomiting. Complete protection from delayed emesis and nausea was achieved in 52-69% of patients that received these prophylactic regimens. Nevertheless, clinical trials have also shown that the addition of metoclopramide or a 5-HT₃ antagonist to dexamethasone gained only a modest benefit over dexamethasone monotherapy for prevention of delayed nausea and vomiting. Dexamethasone monotherapy provides adequate protection against delayed emesis in patients receiving moderate or highly emetogenic chemotherapy.

Based on Phase 2 and Phase 3 clinical trials, the aprepitant regimen demonstrated a consistent statistically significant advantage for the no emesis endpoint in the overall, acute, and delayed phases. However, the results of no nausea were not as robust. Due to its complex metabolic pathway, aprepitant is further evaluated for safety and efficacy in ongoing post-marketing pharmacokinetics and drug-drug interaction studies. Currently, it has not been evaluated in concomitant therapy with dolasetron in clinical trials. Lastly, aprepitant has not been evaluated for prevention of non-chemotherapy related nausea and vomiting, such as postoperative nausea and vomiting.

In conclusion, aprepitant represents a novel therapy for prevention of cisplatin-induced delayed nausea and vomiting. It could be considered as a part of the prophylactic regimen of 5-HT₃ antagonists and corticosteroids in patients receiving highly emetogenic chemotherapy that includes high-dose ($\geq 50\text{mg/m}^2$) cisplatin or in patients receiving highly emetogenic chemotherapy that have failed previous antiemetic prophylactic regimen.

References:

1. Emend Package Insert. Whitehouse Station, New Jersey. Merck & Co., Inc., March 2003.
2. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Ma GJ, Eldridge K, Hipple A, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. *Cancer* 2003;97(12):3090-3098.
3. http://www.fda.gov/cder/foi/nda/2003/21-549_Emend_medr_P3.pdf
4. http://www.fda.gov/cder/foi/nda/2003/21-549_Emend_medr_P2.pdf
5. Chawla SP, Grunberg SM, Gralla RJ, Hesketh PJ, Rittenberg C, Elmer ME, et al. Establishing the dose of the oral NK₁ antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003;97(9):2290-2300.
6. Navari RM, Reinhardt RR, Gralla RJ, Kris MG, Hesketh PJ, Khojasteh A, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *N Engl J Med* 1999;340(3):190-195.
7. Campos D, Pereira JR, Reinhardt RR, Carracedo C, Poli S, Vogel C, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol* 2001;19(6):1759-1767.
8. Cocquyt V, Van Belle S, Reinhardt RR, Decramer MLA, O'Brien M, Schellens JHM, et al. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. *Eur J Cancer* 2001;37:865-842.
9. Van Belle S, Lichinitser MR, Navari RM, Garin AM, Decramer MLA, Riviere A, 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(11):3032-3041.
10. http://www.fda.gov/cder/foi/nda/2003/21-549_Emend_medr_P1.pdf
11. American Society of Health-System Pharmacists. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery.
12. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin Oncol* 1999;17(9):2971-2994.
13. Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989;7:108-114.
14. Gralla RJ, Rittenberg C, Peralta M, Lettow L, Cronin M. Cisplatin and emesis: aspects of treatment and a new trial for delayed emesis using oral dexamethasone plus ondansetron beginning at 16 hours after cisplatin. *Oncology* 1996;53(Suppl 1):86-91.
15. Tsukada H, Hirose T, Yokoyama A, Kurita Y. Randomised comparison of ondansetron plus dexamethasone with dexamethasone alone for the control of delayed cisplatin-induced emesis. *Eur J Cancer* 2001;37:2398-2404
16. The Italian Group For Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med* 2000;342(21):1554-1559.
17. Aapro MS, Thuerlimann B, Sessa C, de Pree C, Bernhard J, Maibach R, et al. A randomized double-blind trial to compare the clinical efficacy of granisetron with metoclopramide, both combined with dexamethasone in the prophylaxis of chemotherapy-induced delayed emesis. *Ann Oncol* 2001;14:291-297.