

**Regence BlueCross BlueShield of Oregon · Regence BlueShield
Regence BlueCross BlueShield of Utah · Regence BlueShield of Idaho
Independent licensees of the Blue Cross and Blue Shield Association**

Medication Policy Manual

Policy No: dru091

Topic: Emend[®], aprepitant

Date of Origin: September 12, 2003

Revised/Effective Date: January 9, 2009

Next Review Date: January 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Aprepitant (Emend[®]) is a medication used to prevent nausea and vomiting resulting from chemotherapy.

Policy/Criteria

- I. Oral aprepitant in quantities up to one 125-mg dose plus two 80-mg doses every two weeks may be considered medically necessary and may be covered without prior authorization.

- II. Oral aprepitant in quantities of up to one 125-mg dose plus two 80-mg doses every week may be considered medically necessary when both criteria A and B below are met:
 - A. The patient is receiving moderately or highly emetogenic chemotherapy (see *Appendix 1*).

 - AND**
 - B. A 5-HT₃ receptor antagonist and corticosteroids are used concomitantly with oral aprepitant (see *Appendix 2*).

III. Administration and Quantity Limitations

- A. Regence considers oral aprepitant to be a self-administered medication.
- B. When prior authorization is approved, aprepitant may be authorized in quantities of up to one, 125-mg dose plus two, 80-mg doses every week. Quantities exceeding one, 125-mg dose plus two, 80-mg doses every week are considered investigational.
- C. Authorization may be reviewed at least every six months to confirm that current medical necessity criteria are met and that the medication is effective.

Position Statement

Summary

- The dose of aprepitant that has been proven to prevent chemotherapy induced nausea and vomiting (CINV) is 125 mg prior to chemotherapy, and 80 mg on days two and three (total of three doses).
- The safety of administering aprepitant more frequently than one treatment course every two to four weeks is currently unknown.

Efficacy

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

- Medications such as ondansetron, granisetron, and dolasetron in combination with dexamethasone have reduced the incidence of vomiting with cisplatin-based chemotherapy regimens from greater than 99% to 50-60%. ^[1, 2] The addition of aprepitant can further reduce the incidence to 22-34% when used as directed. ^[2]

- Aprepitant has demonstrated benefit in the prevention of chemotherapy-induced nausea and vomiting when given with:
 - * High-dose cisplatin-based chemotherapy regimens (highly emetogenic chemotherapy).^[2, 4]
 - * Cyclophosphamide-based chemotherapy regimens used in the treatment of breast cancer. The majority of patients were on a doxorubicin + cyclophosphamide regimen (AC regimen).^[2, 5]
- The combination of several chemotherapy agents with moderate emetogenic risk may result in a regimen that is of high emetogenic risk. Some examples include AC regimens, and FOLFOX in the treatment of colon cancer (oxiplatin plus fluorouracil infusions).
- Aprepitant is dosed 125 mg orally one hour prior to chemotherapy on day one and 80 mg orally once daily on days two and three, along with a corticosteroid, such as dexamethasone, and 5-HT₃ antagonist (dolasetron, granisetron, ondansetron).^[2]
- Aprepitant has not yet been shown to improve adherence to chemotherapy regimens, improve nutritional status, reduce hospitalizations, or ultimately improve the chances of successful chemotherapy.
- It is not clear which patients will benefit most from aprepitant therapy.
- There are currently no efficacy data for repeat administration beyond three doses (125 mg on day one prior to chemotherapy then 80 mg daily on days two and three) per cycle of chemotherapy.

Prevention of Postoperative Nausea and Vomiting

- Aprepitant demonstrated efficacy in the prevention of nausea and vomiting when given as a single 40 mg oral dose one to three hours prior to general anesthesia.^[2]
- A higher dose of aprepitant (125 mg) was no more effective than the 40 mg dose.^[2]
- Aprepitant was not superior to ondansetron 4 mg based on the primary endpoint (no emesis and no rescue therapy 24 hours following surgery).^[2, 10, 11]

Safety

- Aprepitant is a substrate, inhibitor, and inducer of cytochrome P450 (CYP) 3A4, and an inducer of CYP2C9. Aprepitant has clinically significant interactions documented with many medications.^[2]
- The pharmacokinetic characteristics of aprepitant may change with repeat administration, and therefore, its safety profile is subject to change.^[2]
- The safety of administering aprepitant more frequently than one treatment course every two weeks is currently unknown.

- * The majority of the studies with aprepitant have been in chemotherapy regimens that were cycled every three to four weeks. ^[2, 4, 5]
- * A small study has also reported use of aprepitant every two weeks for up to four cycles in patients receiving 'dose-dense' chemotherapy regimens. ^[5, 8]

Aprepitant Use in Other Conditions

- Aprepitant has not been studied for the treatment of established nausea and vomiting. ^[2]
- Aprepitant was not effective in treating major depressive disorder in five controlled clinical trials. ^[9]

Appendix 1: National Comprehensive Cancer Network (NCCN): Emetogenic potential of antineoplastic agents.

HIGH EMETIC RISK (> 90% FREQUENCY OF EMESIS)

a.	AC combination regimen (defined as either doxorubicin or epirubicin with cyclophosphamide)
b.	Altretamine
c.	Carmustine > 250 mg/m ²
d.	Cisplatin ≥ 50 mg/ m ²
e.	Cyclophosphamide > 1,500 mg/ m ²
f.	Dacarbazine
g.	Mechlorethamine
h.	Procarbazine (oral)
i.	Streptozocin

MODERATE EMETIC RISK (30 TO 90% FREQUENCY OF EMESIS)

a.	Aldesleukin > 12 to 15 mu/m ²	n.	Daunorubicin
b.	Amifostine > 300 mg	o.	Epirubicin
c.	Arsenic trioxide	p.	Etoposide (oral)
d.	Azacitidine	q.	Idarubicin
e.	Busulfan > 4 mg/d	r.	Ifosfamide
f.	Carboplatin	s.	Imatinib (oral)
g.	Carmustine ≤ 250 mg/m ²	t.	Irinotecan
h.	Cisplatin < 50 mg/m ²	u.	Lomustine
i.	Cyclophosphamide ≤ 1,500 mg/m ²	v.	Melphalan > 50 mg/m ²
j.	Cyclophosphamide (oral)	w.	Methotrexate 250 to 1000 mg/m ²
k.	Cytarabine > 1 Gm/m ²	x.	Oxaliplatin > 75 mg/m ²
l.	Dactinomycin	y.	Temozolomide (oral)
m.	Doxorubicin	z.	Vinorelbine (oral)

Appendix 2: Prevention of nausea and vomiting with highly emetogenic chemotherapy ^[6]

Aprepitant 125 mg PO on day 1 (or fosaprepitant 115 mg IV), 80 mg PO on days 2 and 3.

AND

Dexamethasone 12 mg PO or IV on day 1, 8 mg PO or IV on days 2 through 4

AND

5-HT₃ antagonist:

* Ondansetron 16 to 24 mg PO or 8 to 12 mg (maximum 32 mg) IV on day 1.

OR

* Granisetron 2mg PO or 1 mg PO BID or 0.01 mg/kg (maximum 1mg) IV day 1 or transdermal patch containing 34.3 mg granisetron applied 24 to 48 hours in advance.

OR

* Dolasetron 100 mg PO or 1.8 mg/kg IV or 100 mg IV on day 1.

OR

* Palonosetron 0.5 mg PO or 0.25 mg IV day 1.

AND

Lorazepam 0.5 to 2 mg PO or IV or sublingual every 4 to 6 hours as needed on days 1 - 4.

References

1. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol.* 1999;17(9):2971-94.
2. Emend[®] (aprepitant) prescribing information. Merck and Co.; Whitehouse Station, NJ, April 2008.
3. Poli-Bigelli S, et al. 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. *Cancer.* 2003;97:3090-8.

4. Hesketh PJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – The Aprepitant Protocol 052 Study Group. *J Clin Oncol*. 2003;21(22):4112-9.
5. Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol*. 2005;23(12):2822-30.
6. National Comprehensive Cancer Network (NCCN); Clinical practice Guidelines in Oncology: Antiemesis – v.1.2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.
7. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, et al. American Society of Clinical Oncology Guideline for antiemetics in oncology: update 2006. *J Clin Oncol*. 2006;24:2932-47.
8. Herstedt J, Muss HB, Warr DG, Hesketh PJ, Eisenberg PD, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer*. 2005;104(7):1548-55.
9. Keller M, Montgomery S, Ball W, Morrison M, Snavely D, et al. Lack of efficacy of the substance P (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry*. 2006;59:216-23.
10. Gan TJ, Apfel CC, Kovac A, Philip BK, Singla N, et al.; Aprepitant-PONV Study Group. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth Analg*. 2007;104(5):1082-9.
11. Diemunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, et al.; Aprepitant-PONV Protocol 091 International Study Group. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. *Br J Anaesth*. 2007;99(2):202-11.

Cross References
Aloxi [®] , palonosetron dru163
Anzemet [®] , dolasetron dru069
Kytril [®] , granisetron dru068
Sancuso [®] , granisetron topical patch dru164
Zofran [®] , ondansetron dru046

Codes	Number	Description
N/A		