**Aprepitant (Emend®)**

[Developed, December 2003; Revised, January 2006; February 2006; October 2009; September 2011; June 2013; August 2013]

**M EDICAID DR UG USE REVIEW CRITERIA FOR OUTPATIENT USE**

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with [*].

1. **Dosage**

   **Adults**
   
   Current therapies for chemotherapy induced nausea/vomiting (CINV) and post-operative nausea and vomiting (PONV) target corticosteroid, dopamine, and serotonin (5-HT₃) receptors. In the central nervous system, tachykinins and neurokinins play a role in some autonomic reflexes and behaviors. Aprepitant is a selective human substance P/neurokinin 1 (NK₁) antagonist with a high affinity for NK₁ receptors and little, if any, attraction for corticosteroid, dopamine, or 5-HT₃ receptors. Aprepitant is FDA-approved for prevention of CINV due to high and moderate emetogenic agents including high dose cisplatin, as well as prevention for PONV. When used to prevent CINV with highly emetogenic chemotherapy, aprepitant is generally prescribed in combination with a 5-HT₃ receptor antagonist and corticosteroids based on data from available published anti-emetic guidelines. Maximum recommended doses for aprepitant are summarized in Table 1. Dosages exceeding those listed in Table 1 will be reviewed.

   **Table 1**
   
<table>
<thead>
<tr>
<th>INDICATION</th>
<th>MAXIMUM RECOMMENDED DOSE</th>
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<tbody>
<tr>
<td>CINV:</td>
<td></td>
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<tr>
<td>aprepitant (Emend®)</td>
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<tr>
<td>day 1</td>
<td>125 mg/day*</td>
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<tr>
<td>days 2 and 3</td>
<td>80 mg/day</td>
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<td>PONV:</td>
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<tr>
<td>aprepitant within 3 hours of anesthesia induction</td>
<td>40 mg as a single dose</td>
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</tbody>
</table>

   *doses up to 400 mg have been used in clinical trials

   **Pediatrics**
   
   Aprepitant is not recommended for use in pediatric patients because safety and efficacy have not been established in children.

2. **Duration of Therapy**

   The maximum treatment duration for aprepitant is three days per chemotherapy cycle for moderately or highly emetogenic chemotherapy regimens. Chemotherapy regimens are administered for one to several days within a 30-day time period and repeated in cycles. The number of cycles varies based on the type of cancer being treated. Unless otherwise specified, aprepitant treatment regimens continuing for greater than three days per chemotherapy cycle will be reviewed for appropriateness of use.

3. **Duplicative Therapy**

   Aprepitant is the first medication in the class of selective human substance P/NK₁ antagonists. Fosaprepitant, the injectable formulation of aprepitant, is only indicated for use on day 1 of the
chemotherapy cycle as the 115 mg dose with oral aprepitant administered on days 2 and 3. Fosaprepitant 150 mg injection is not administered with oral aprepitant on any treatment days. Dosage regimens incorporating concurrent use of fosaprepitant 150 mg and aprepitant or more than one day of fosprepitant 115 mg therapy in conjunction with two days of oral apremitant will be reviewed.

4. * Drug-Drug Interactions

Patient profiles will be monitored to identify regimens that may have clinically significant drug-drug interactions.
Drug-drug interactions considered clinically relevant for apremitant are summarized in Table 2. Only those interactions classified as clinical significance level 1, contraindicated, or life threatening which have not been classified will be reviewed:
<table>
<thead>
<tr>
<th>TARGET DRUG</th>
<th>INTERACTING DRUG</th>
<th>INTERACTION</th>
<th>RECOMMENDATION</th>
<th>CLINICAL SIGNIFICANCE*+</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprepitant</td>
<td>CYP3A4 inducers (e.g., carbamazepine, rifampin)</td>
<td>adjunctive use may induce aprepitant metabolism and potential for reduced aprepitant serum levels and decreased aprepitant efficacy; CYP3A4 inducer activity may also be reduced, as aprepitant is also a CYP3A4 inducer</td>
<td>monitor patients for aprepitant efficacy, and, if necessary, modify aprepitant dose or choose alternative anti-emetic that does not interact with CYP3A4 inducers; monitor CYP3A4 inducer activity and adjust dose as necessary</td>
<td>moderate (DrugReax) 3-moderate (CP)</td>
</tr>
<tr>
<td>aprepitant</td>
<td>CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, nefazodone, clarithromycin, ritonavir)</td>
<td>combined administration may result in reduced aprepitant metabolism, increased serum aprepitant levels, and the potential for adverse effects; however, aprepitant appears to be tolerated over a wide dosage range and is prescribed for short time periods</td>
<td>clinical significance of interaction not well defined; observe patients for increased aprepitant adverse effects and adjust dose if necessary</td>
<td>major (DrugReax) 3-moderate (CP)</td>
</tr>
<tr>
<td>aprepitant</td>
<td>CYP3A4 substrates (e.g., aripiprazole, diltiazem, ranolazine, ziprasidone)</td>
<td>combined use may result in elevated substrate plasma levels and potential for toxicity or loss of efficacy, as aprepitant is known CYP3A4 inhibitor and inducer and may interfere with metabolism of medications metabolized by CYP3A4</td>
<td>use aprepitant cautiously with compounds metabolized by CYP3A4; monitor patients carefully for signs and symptoms of substrate toxicity or loss of efficacy and adjust substrate dose as necessary</td>
<td>major (DrugReax) 2-major, 3-moderate (CP) 2 (DIF)</td>
</tr>
<tr>
<td>aprepitant</td>
<td>oral contraceptives (OC)</td>
<td>adjunctive use may result in reduced OC efficacy as AUC for both estrogen and progestin components may be reduced; mechanism unknown</td>
<td>alternative or back-up methods of contraception recommended during time that aprepitant is prescribed and for one month following last aprepitant dose</td>
<td>moderate (DrugReax) 2-major (CP)</td>
</tr>
<tr>
<td>aprepitant</td>
<td>pimozide (Orap®)</td>
<td>concurrent administration may result in elevated plasma pimozide levels and increased risk for QT interval prolongation, cardiac arrhythmias as aprepitant inhibits CYP3A4, the enzyme responsible for pimozide metabolism</td>
<td>adjunctive use contraindicated</td>
<td>contraindicated (DrugReax) 1-severe (CP) 1 (DIF)</td>
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<tr>
<td>aprepitant</td>
<td>warfarin</td>
<td>co-administration may result in significant decreases in warfarin serum levels, INR and warfarin efficacy, as aprepitant induces CYP2C9, the enzyme responsible for warfarin metabolism</td>
<td>monitor clotting status closely within 2-week period (especially 7 to 10 days) after each 3-day chemotherapy regimen or following single-dose therapy for PONV</td>
<td>major (DrugReax) 2-major (CP) 4 (DIF)</td>
</tr>
</tbody>
</table>

*CP = Clinical Pharmacology  +Drug Interaction Facts
REFERENCES


Prepared by: Drug Information Service, The University of Texas Health Science Center at San Antonio, and the College of Pharmacy, The University of Texas at Austin.

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