Delayed-Release Doxylamine-Pyridoxine (Diclegis)
Abbreviated National Drug Monograph
March 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

<table>
<thead>
<tr>
<th>Description</th>
<th>Diclegis is a fixed-dose, delayed-release combination of doxylamine succinate (antihistamine) and pyridoxine hydrochloride (vitamin B6). Though Diclegis is similar to Bendectin, removed from the U.S. market in 1983, the reformulated product uses modern technology for a delayed release mechanism and is also lactose-free.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication(s) Under Review in this document (may include off label)</td>
<td>Delayed-release doxylamine-pyridoxine is FDA approved for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management.</td>
</tr>
<tr>
<td>Dosage Form(s) Under Review</td>
<td>Delayed-release tablets 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride</td>
</tr>
<tr>
<td>REMS</td>
<td>☒ No REMS</td>
</tr>
<tr>
<td>Pregnancy Rating</td>
<td>FDA Category A: the drug is intended for use in pregnant women.</td>
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</tbody>
</table>

Executive Summary

Efficacy

- In the trial reviewed for FDA approval, delayed-release doxylamine-pyridoxine was statistically superior to placebo in improving nausea and vomiting symptoms as assessed by reduction in the PUQE (pregnancy unique quantification of emesis) score (-4.8 with delayed-release doxylamine-pyridoxine vs. -3.9 with placebo; difference 0.9 on 15 point scale; p=0.006) and in global assessment well-being scores in women with NVP after two weeks of treatment.
- Compared to oral ondansetron 4 mg every 8 hours, non-delayed-release doxylamine 12.5 mg plus pyridoxine 25 mg every 8 hours was less effective at reducing nausea and vomiting symptoms after 5 days of treatment as assessed by a 100-mm visual analog scale (VAS), though both therapies were associated with improvements.
- Delayed-release doxylamine-pyridoxine was associated with slight but statistically significantly greater improvements in PUQE symptom scores compared to pyridoxine alone in a matched cohort study.

Safety

- Delayed-release doxylamine-pyridoxine is contraindicated with monoamine oxidase inhibitors (MAOIs) because of the risk of prolonging and intensifying adverse central nervous system effects of doxylamine.
- Somnolence and sedation may occur as a side effect of doxylamine; somnolence was the only adverse event reported more frequently than placebo and in more than 5% of patients in the phase 3 clinical trial of 2 weeks’ duration.
- Due to the anticholinergic properties of doxylamine, delayed-release doxylamine-pyridoxine should be used with caution in women with medical conditions where anticholinergic effects are of concern.
- The combination of doxylamine and pyridoxine has been available for decades and has been extensively studied in pregnant women with NVP. Large meta-analyses have identified no increase in adverse fetal effects, and the drug is considered safe in pregnancy.

Other Considerations

- Off-label use of OTC 12.5 mg doxylamine (0.5 tablets of 25 mg strength) plus 10...
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The purpose of the review is to evaluate the safety and efficacy of the recently FDA approved product Diclegis, the only FDA indicated product for the treatment of NVP in the U.S. Bendectin, originally FDA approved for NVP in the 1950s as a combination of doxylamine, pyridoxine, and dicyclomine, was reformulated in the 1970s without dicyclomine after the DESI (Drug Efficacy Study Implementation) review found dicyclomine to be ineffective for NVP. In 1983, Bendectin was voluntarily withdrawn from the market due to the financial burden of pending law suits against the manufacturer alleging birth defects were caused by the drug. FDA reviewed all available data and concluded that Bendectin was not withdrawn for safety concerns or lack of effectiveness.2

The same reformulated, delayed release product as Diclegis has been available in Canada known as Diclectin since 1979.3

**Issues to be determined:**
- Does delayed-release doxylamine-pyridoxine improve NVP?
- Does delayed-release doxylamine-pyridoxine offer advantages to currently available alternatives?
- Does delayed-release doxylamine-pyridoxine offer advantages over current VANF agents?
- What safety issues need to be considered with the use of delayed-release doxylamine-pyridoxine?
- Does delayed-release doxylamine-pyridoxine have specific characteristics best managed by the non-formulary process or criteria for use?

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Potential Impact
- Delayed-release doxylamine-pyridoxine is the only FDA approved treatment for NVP.
- NVP occurs commonly during pregnancy (about 70%), typically beginning at about 5 weeks’ gestation, peaking at 9 weeks’ gestation, and usually subsiding by 16 to 20 weeks’ gestation; however about 15-20% continue to have symptoms into the third trimester, with some women experience persistent NVP until delivery.
- Doxylamine plus pyridoxine provides a modest but statistically significant benefit in the treatment of NVP. Evidence available from decades of exposure shows that doxylamine-pyridoxine is not associated with teratogenicity. It is reasonable to consider doxylamine-pyridoxine in women with NVP who are seeking treatment and have failed lifestyle modifications and nonpharmacologic options.
- Delayed-release doxylamine-pyridoxine offers women a single tablet containing two ingredients; however, 2 tablets are taken at bedtime, and up to 4 tablets taken three times a day may be required.
### Other therapeutic options

(Further discussion under Place In Therapy section)

<table>
<thead>
<tr>
<th>Formulary Alternatives</th>
<th>Other Considerations</th>
</tr>
</thead>
</table>
| **Pyridoxine (vitamin B6)** | - OTC vitamin; off-label for NVP  
- Evidence supports some effect in NVP  
- Well recognized as safe and non-teratogenic  
- Doses vary: 10 – 25 mg three to four times daily  
- 50 mg and 100 mg on FSS pricing |

| **Ondansetron** | - Rx; off-label for NVP  
- Evidence supports effect in NVP and HG, particularly with emesis  
- Safety data in human pregnancy is less clear than with other listed alternatives  
- Dose: 4 mg orally every 8 hrs  
- Intravenous route also an option  
- Adverse effects: headache, constipation, sedation  
- Per ACOG NVP algorithm, recommended use only after failure of other options in patients with dehydration |

<table>
<thead>
<tr>
<th><strong>Non-formulary Alternatives</strong></th>
<th>Other Considerations</th>
</tr>
</thead>
</table>
| **Doxylamine** | - OTC antihistamine; single agent use is off-label for NVP  
- Sedating antihistamine FDA approved for insomnia (tablets) and allergies (liquid)  
- For NVP mostly studied in combination with pyridoxine; evidence supports modest effect in NVP  
- Available as 25 mg, scored tablet  
- No single agent product is available on FSS  
- Dosing recommended by ACOG: 12.5 mg three or four times daily as add-on therapy when pyridoxine monotherapy unsuccessful (prior to approval of Diclegis) |

### Efficacy (FDA Approved Indications)

**Literature Search Summary**

A literature search was performed on PubMed/Medline (1966 to August 2014) using the search terms <Diclegis> and <doxylamine and pyridoxine and nausea>. Randomized controlled trials published in peer-reviewed journals evaluating the FDA approved indication were included. Medical reviews on the FDA website were also reviewed for additional information.

**Review of Efficacy**

- The FDA approval of Diclegis was based on one new phase 3 clinical trial as well as pharmacokinetic studies using the to-be-marketed formulation. Although conducting bioequivalence studies using the original product...
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Updated March 2015
Updated version may be found at www.pbm.va.gov or PBM INTRAnet

(Bendectin) tablets was not possible, the FDA considered the totality of data available with Bendectin as well as the individual ingredients. Two additional relevant studies published after FDA review are also summarized below.

- Results from Study DIC-301 showed a statistically significant improvement in nausea and vomiting symptoms as measured by the PUQE (pregnancy unique quantification of emesis) score as well as improvements in global assessment well-being scores after two weeks of treatment with delayed-release doxylamine-pyridoxine compared to placebo.
- In a direct comparison study of oral preparations of non-delayed release doxylamine plus pyridoxine and ondansetron, ondansetron was associated with greater improvements in nausea and vomiting symptoms according to a 100-mm visual analog scale (VAS) score, though both treatment groups reported improvements. More women treated with ondansetron experienced clinically significant improvements in VAS scores defined as at least a 25-mm change.
- Compared to monotherapy with pyridoxine, slight but statistically significantly greater improvements in PUQE symptom scores were observed with pregnant women who received delayed-release doxylamine-pyridoxine in a matched cohort study.
- Overall, there is a moderate quality of evidence for the use of delayed-release doxylamine-pyridoxine for women with NVP. (Refer to Appendix A).

Study DIC-301 - Delayed-release doxylamine-pyridoxine vs. placebo for NVP

- Study DIC-301 was a phase 3, double-blind, multicenter, placebo-controlled, industry supported trial that randomized 280 pregnant women with a confirmed singleton pregnancy and gestational age of 7-14 weeks, NVP (and PUQE score ≥6), and failure of conservative treatment (dietary and lifestyle modifications) to delayed release doxylamine-pyridoxine or similar appearing placebo for 14 days.
- Study drug was given at a dose of two tablets at bedtime and titrated up to a maximum of four tablets daily. The primary endpoint was the change in PUQE score, a 2-part, validated scoring system that incorporates physical symptoms and quality of life with NVP. The symptom domain ranges from 3 points (no symptoms) to 15 points (most severe) and incorporates 1) duration of nausea for 1-5 points; 2) vomiting episodes for 1-5 points, and 3) retching/dry heave episodes for 1-5 points over the past 24 hours. The quality of life domain is a 10 point scale of overall well-being, with zero being the worst and 10 being the best possible. Women self-reported PUQE symptom scores daily and global well-being assessment weekly in the study diary.
- Baseline (mean): age 26 yrs; gestational age at enrollment 9.3 weeks; PUQE symptom score 9; PUQE overall well-being 5; Caucasian 60%; dose: 4 tabs daily 60%; 3 tabs daily 21%; 2 tabs daily 19%. Five patients from each group discontinued due to adverse events.
- Results: In the intention to treat population, delayed-release doxylamine-pyridoxine was associated with statistically greater improvements in PUQE symptom scores and global assessment well-being score compared to placebo. More women requested continued compassionate use of delayed release doxylamine-pyridoxine than placebo at the end of the trial. There was a trend toward more lost employment with placebo.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Delayed-release doxylamine-pyridoxine N=131</th>
<th>Placebo N=128</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ PUQE score*</td>
<td>-4.8 ±2.7</td>
<td>-3.9 ±2.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Δ Well-being global assessment *</td>
<td>+2.8 ±2.8</td>
<td>+1.8 ±2.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Time loss from employment (days)</td>
<td>0.92±3.86</td>
<td>2.37±10.23</td>
<td>0.06</td>
</tr>
<tr>
<td>Pts requesting cont’d compassionate use after study</td>
<td>48.9%</td>
<td>32.8%</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*change from baseline to Day 15

Additional studies:
Doxylamine and pyridoxine vs. ondansetron for NVP

- The efficacy and safety of doxylamine 12.5 mg plus pyridoxine 25 mg (as individual components; non-Diclegis preparation) vs. ondansetron 4 mg were compared in a small, single-center, double-blind, randomized controlled trial of 5 days’ duration. Study drugs were instructed to be taken every 8 hours. Nausea and emesis were rated by patients on a 100-mm VAS that has been validated in non-pregnant patient populations. Women were not counseled on lifestyle and nonpharmacologic treatment of NVP.
• **Baseline:** 30 of 36 randomized women with a median gestational age of 8 weeks completed the study; pyridoxine and doxylamine VAS scores – nausea 81, emesis 64; ondansetron VAS scores – nausea 73, emesis 53. Adherence was 77% in both groups.

• **Results:** Ondansetron was associated with statistically significantly greater reductions in the VAS scores for nausea (primary endpoint) and emesis, though improvements were noted in both treatment groups. Using a predefined value of a difference of 25-mm as clinically significant, the majority of patients receiving ondansetron reported clinically significant improvements in nausea and emesis, while less than half of the patients receiving doxylamine and pyridoxine reported clinically significant improvements.

### Doxylamine and pyridoxine vs. ondansetron results\(^9\)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Doxylamine and pyridoxine N=17</th>
<th>Ondansetron N=13</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in nausea VAS score (median)</td>
<td>20 (95% CI 8-47)</td>
<td>51 (95% CI 36-65)</td>
<td>0.019</td>
</tr>
<tr>
<td>Reduction in emesis VAS score (median)</td>
<td>17 (95% CI 0-36)</td>
<td>41 (95% CI 19-56)</td>
<td>0.049</td>
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<tr>
<td>≥25-mm reduction in nausea VAS score, n(%)</td>
<td>7 (41%)</td>
<td>12 (92%)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥25-mm reduction in emesis VAS score, n(%)</td>
<td>6 (35%)</td>
<td>10 (77%)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

*median reduction; VAS=visual analog score, 100-mm scale

### Delayed-release doxylamine-pyridoxine vs. pyridoxine\(^10\)

- The effect of delayed-release doxylamine-pyridoxine was compared to pyridoxine monotherapy in a matched cohort study including 80 cases per arm using data from the Motherisk NVP helpline (industry supported) in Ontario, Canada. Study participants were pregnant women seeking telephone counseling for NVP and had a mean age of 32 years, gestational age of 8 weeks, and baseline PUQE score of 8 (range of 3 to 15, with 3 being no symptoms and 15 being the most severe). The mean daily dose of delayed-release doxylamine-pyridoxine was 3.79 tablets, and women in the pyridoxine monotherapy group used an average of 99 mg/day. For the primary endpoint, the overall mean change in PUQE score over 1 week was -0.2 (denoting worsening) in pyridoxine patients and +0.5 in delayed-release doxylamine-pyridoxine patients, a between-group difference that was statistically significant. More pronounced differences in improvements were noted in women with higher baseline PUQE scores.

### Potential Off-Label Use

- None identified other than potential use of the product before failure of lifestyle and nonpharmacologic treatment.

### Safety

*(for more detailed information refer to the product package insert)*

<table>
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<tr>
<th>Comments</th>
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<tbody>
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<td><strong>Boxed Warning</strong></td>
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<tr>
<td><strong>Contraindications(^1)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Warnings/Precautions(^1)</strong></td>
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</tbody>
</table>
| | Due to the anticholinergic properties of doxylamine, delayed-release
doxylamine-pyridoxine should be used with caution in women with concomitant medical conditions where anticholinergic effects are of concern: asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.

Safety Considerations
- The combination of doxylamine and pyridoxine has been available for decades and has been extensively studied for identification of a safety signal related to potential teratogenicity. Two large meta-analyses, one including 27 studies published between 1963 and 1991, and the other including 17 studies published between 1963 and 1985 revealed no statistically significant associations between first trimester exposure of doxylamine and pyridoxine (with or without dicyclomine) and fetal abnormalities.
- Briggs Drugs in Pregnancy and Lactation rates the combination of doxylamine-pyridoxine as safe in human pregnancy, including the first trimester.

Adverse Reactions
- Common adverse reactions
  - Incidence ≥5% and higher than placebo: somnolence (14% vs. 12%)

Death/Serious adverse reactions
- Per FDA review, a total of four serious adverse events were reported in delayed-release doxylamine-pyridoxine group in study DIC-301 (vs. 5 in the placebo arm) within the 30 day follow-up window of completion of the study or during the first 30 days after continued compassionate use. The events reported were similar between treatment groups and mostly related to pregnancy, persperium, and perinatal conditions. The 3 cases of missed or spontaneous abortion and 1 intrauterine death that occurred in the delayed-release doxylamine-pyridoxine group were classified as not related or unlikely related to study drug.

Discontinuations due to adverse reactions
- 3.8% (vs. 3.9% in the placebo arm)

Drug Interactions
- Drug-Drug Interactions
  - MAOIs – contraindicated; prolong and intensify anticholinergic effects of doxylamine
  - Central nervous system depressants (including alcohol) – concurrent use not recommended

Drug-food Interactions
- Food delays and may reduce the absorption of delayed-release doxylamine-pyridoxine. Delayed-release doxylamine-pyridoxine should be taken on an empty stomach with a glass of water.

Risk Evaluation
As of March 13, 2015

Comments
- Sentinel event advisories: None

Look-alike/sound-alike error potentials

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexi-Comp</th>
<th>ISMP</th>
<th>Clinical Judgment</th>
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<tr>
<td>Doxylamine-Pyridoxine</td>
<td>doxycycline, paroxetine, pralidoxime, Pyridium</td>
<td>Pyridium</td>
<td>dicyclomine</td>
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<tr>
<td>DICLEGIS</td>
<td>None</td>
<td>None</td>
<td>None</td>
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</tbody>
</table>

- Sources: Based on clinical judgment and an evaluation of LASA information from two data sources (Lexi-Comp and ISMP Confused Drug Name List)
Other Considerations

The rationale for the delayed release formulation is based on taking 2 tablets at bedtime for therapeutic levels in the morning when NVP are usually maximal.12 The anti-emetic effects of the delayed-release product occur four to six hours after administration. If additional doses are needed, routine administration rather than as needed is recommended to provide more sustained effects throughout the day.13

Dosing and Administration1

- The initial recommended starting dose of delayed-release doxylamine-pyridoxine is two tablets orally at bedtime (Day 1). If symptoms are adequately controlled the next day, the same dose should be continued. If symptoms persist, the dose may be titrated over days up to a maximum of four tablets daily (one tablet in the morning, one tablet in the mid-afternoon, and two tablets at bedtime). Refer to the package insert for full dosing information on the recommended dose titration schedule.
- Delayed-release doxylamine-pyridoxine should be taken on an empty stomach with a glass of water.
- The extended release tablets must be swallowed whole and cannot be crushed, chewed, or split.

Special Populations (Adults)1

<table>
<thead>
<tr>
<th>Comments</th>
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<tr>
<td>Renal Impairment</td>
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<tr>
<td>Hepatic Impairment</td>
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<tr>
<td>Pharmacogenetics/genomics</td>
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</tbody>
</table>

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting)

- NVP occurs commonly during pregnancy, with two recent meta-analyses reporting prevalence rates of about 70% both globally and within the U.S.14,15
- NVP typically begins in the first trimester of pregnancy at about 5 weeks of gestation and peaks at 9 weeks of gestation.16 In most women, the condition is self-limiting and resolves by 16 to 20 weeks of gestation. In 15 to 20% of women, symptoms may persist into the third trimester. An estimated 35% of women have symptoms considered to be clinically relevant.17 A more severe form of nausea and vomiting during pregnancy called hyperemesis gravidarum (HG) occurs rarely in about 1% of pregnant women and is characterized by persistent vomiting, a greater than 5% loss of pre-pregnancy weight, dehydration, electrolyte imbalance and ketosis and often requires hospital admission.17 Additional complications of HG to the mother include vitamin deficiencies, Mallory-Weiss tears of the esophagus, and postpartum complications. HG may result in fetal growth restriction and prematurity.17
- Non-pharmacologic diet and lifestyle changes are recommended first line. The addition of pharmacologic therapy may be considered if nonpharmacologic measures are unsuccessful.
- Since pregnant women are often excluded from clinical trials, data are overall limited on the efficacy and safety of most medications, including those used for NVP. There is inadequate evidence to support a particular intervention.5
- Guidelines
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- American College of Obstetrician Gynecologists Practice Bulletin (2004)⁵: These guidelines were written before the re-introduction of Diclegis into the U.S. market. The recommended hierarchy is based on balancing benefit and risk. Early use of a multivitamin may prevent or reduce NVP. Monotherapy with pyridoxine 10-25 mg (OTC) three or four times daily is recommended as first-line pharmacologic treatment, after failure of lifestyle and dietary modifications. If NVP persists, doxylamine 12.5 mg (0.5 tablet of OTC product) three or four times daily may be added. If unsuccessful, promethazine (12.5-25 mg every four hours orally or rectally) or dimenhydrinate (50-100 mg every four to six hours orally or rectally) may be added. Third-line options for women who continue to have NVP include metoclopramide, trimethobenzamide, corticosteroids, and ondansetron.

- Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines (2002)¹⁸: After incorporation of lifestyle modifications, combination therapy with doxylamine 10 mg/pyridoxine 10 mg (up to four tablets daily) should be the “standard of care” first-line pharmacologic treatment because of the greatest evidence to support efficacy and safety. If NVP persists, dimenhydrinate (50-100 mg every four or six hours orally or rectally) or promethazine 5-10 mg every six or eight hours orally or rectally) may be added. For more severe NVP unresponsive to these measures, phenothiazines are considered safe and effective, followed by metoclopramide which is considered safe (efficacy support is less clear), and then corticosteroids for refractory cases (avoid in first trimester due to risk of oral clefting). Ondansetron is listed in last place in the algorithm because of insufficient safety evidence for first trimester exposure. Alternative therapies (e.g., ginger, acupuncture, and acupressure) may be effective and considered at any point in the algorithm.

- Doxylamine plus pyridoxine provides a modest but statistically significant benefit in the treatment of NVP. Evidence available from decades of exposure shows that doxylamine-pyridoxine is not associated with teratogenicity during first trimester exposure. It is reasonable to consider doxylamine-pyridoxine in women with NVP who are seeking treatment and have failed lifestyle modifications and nonpharmacologic options.

- Overall, there is a moderate quality of evidence for the use of delayed-release doxylamine-pyridoxine for women with NVP (Refer to Appendix A as well as sections on Efficacy).

- Off-label use of OTC 12.5 mg doxylamine (0.5 tablets of 25 mg strength) plus 10 to 25 mg pyridoxine taken three to four times daily offers a lower cost alternative to the combined, delayed-release product. This regimen has been used in the U.S. in the absence of a combination product and is recommended in the ACOG 2004 NVP Guidelines. A disadvantage is increased pill burden to the patient (2 pills instead of 1 pill per dose), which may be significant for some patients in the setting of nausea and vomiting. Pill splitting of the single ingredient product(s) is required to obtain a similar dose as the delayed release combination product. The clinical significance of the differences in pharmacokinetics using the immediate release products compared to the delayed release combination product is unclear.

Prepared March 2015. Contact person: Lisa Longo, Pharm.D., BCPS Pharmacy Benefits Management Services
References

## Appendix A: GRADEing the Evidence

<table>
<thead>
<tr>
<th>Quality of evidence designation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>High</strong></td>
<td>Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with &gt; 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.</td>
</tr>
</tbody>
</table>