Formulary Drug Reviews

Doxylamine Succinate/Pyridoxine Hydrochloride

Dennis J. Cada, PharmD, FASHP, FASCP (Editor)*; Kendra Demaris, PharmD[†];
Terri L. Levien, PharmD[‡]; and Danial E. Baker, PharmD, FASHP, FASCP[§]

Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available online. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The October 2013 monograph topics are afatinib, ferric carboxymaltose, cangrelor, vedolizumab, and albiglutide. The DUE/MUE is on afatinib.

Generic Name: Doxylamine Succinate/Pyridoxine Hydrochloride Delayed-Release Tablets

Proprietary Name: Diclegis (Duchesnay Inc)

Approval Rating: 5S

Therapeutic Class: Antiemetic

Similar Drugs: Doxylamine and Pyridoxine

Sound- or Look-Alike Names: *Diclectin*

INDICATIONS

Diclegis is approved for the treatment of nausea and vomiting in pregnant women who do not respond to conservative management.¹

Bendectin was approved in the United States for the same indication in 1956, with the original formulation consisting of dicyclomine hydrochloride, doxylamine succinate, and pyridoxine hydrochloride. Subsequent reformulation of the product in 1976 removed the dicyclomine component. Marketing of the product was discontinued in June 1983 due to allegations of significant teratogenicity associated with in utero exposure.

A large number of lawsuits alleged that *Bendectin* caused birth defects, primarily limb reduction defects. The manufacturer cited that product discontinuation was due to increased insurance costs of maintaining the product in a litigious drug market.^{2,3} The combination formula of delayed-release doxylamine succinate and pyridoxine hydrochloride has been available as *Diclectin* in Canada since 1979 for the treatment of nausea and vomiting during pregnancy.^{4,5}

First-line treatment recommendations for nausea and vomiting during pregnancy per the American College of Obstetricians and Gynecologists (ACOG) include pyridoxine or pyridoxine plus doxylamine.⁶ Review articles on the treatment of nausea and vomiting during pregnancy, prior to the approval of doxylamine/pyridoxine, have recommended initial treatment with pyridoxine (vitamin B6). If that was inadequate, doxylamine could be added to the drug regimen. If these measures were inadequate, promethazine or dimenhydrinate could be substituted for the doxylamine. Additional medicinal measures, including the use of oral or intravenous (IV) metoclopramide, oral trimethoprim, oral or IV ondansetron, intramuscular promethazine, or methylprednisolone, were suggested if the problem was not resolved.^{4,7}

*Founder and Contributing Editor, *The Formulary*; [†]Junior Specialist, Department of Pharmacy Practice, Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo; [‡]Clinical Associate Professor of Pharmacotherapy, Drug Information Center, Washington State University, Spokane, Washington; [§]Director, Drug Information Center, and Professor of Pharmacy Practice, College of Pharmacy, Washington State University, PO Box 1495, Spokane, Washington 99210-1495. *The authors indicate no relationships that could be perceived as a conflict of interest.*

Diclegis is not approved for the treatment of hyperemesis gravidarum.¹

CLINICAL PHARMACOLOGY

The mechanism of action of doxylamine succinate and pyridoxine hydrochloride (a vitamin B6 analog) in treating nausea and vomiting in pregnant women is unknown.¹

PHARMACOKINETICS

Pharmacokinetic studies described in the product labeling have been conducted in healthy nonpregnant adult women.¹ Both drugs are absorbed in the gastrointestinal (GI) tract, mainly in the jejunum. Peak plasma concentrations of doxylamine occur within 7.5 hours, and peak plasma concentrations of pyridoxine occur within 5.5 hours with the delayed-release tablet formulation. The half-life of doxylamine was 10.1 hours following a single dose and 11.9 hours following multiple doses. The half-life of pyridoxine was 0.5 hours following both single- and multiple-dose administration.^{1,8} Doxylamine is metabolized by the liver to N-desmethyldoxylamine and N,N-didesmethyldoxylamine. Both of these metabolites are excreted by the kidney. Pyridoxine is a prodrug that is primarily metabolized in the liver to 5 active metabolites.¹

Administration with food significantly reduces the bioavailability of pyridoxine. Food decreased both the peak plasma concentrations and the area under the curve (AUC) by approximately 50%.¹

No pharmacokinetic studies have been conducted in patients with hepatic or renal impairment.¹

A study conducted in Canada found no differences in the pharmacokinetics of doxylamine or pyridoxine in nonpregnant women of reproductive age and women in the first trimester of pregnancy.⁹

COMPARATIVE EFFICACY

Indication: Nausea and Vomiting of Pregnancy

Guidelines

Guideline: ACOG Practice Bulletin: Nausea and vomiting of pregnancy

Reference: ACOG, 2004⁶

Comments: First-line pharmacologic treatment option is vitamin B6 or vitamin B6 plus doxylamine. Recommendations for refractory nausea and vomiting of pregnancy include antihistamine H₁ receptor antagonists, phenothiazines, and benzamides.

Studies

Drug: Pyridoxine/Doxylamine vs Metoclopramide

Reference: Ashkenazi-Hoffnung L, et al, 2013¹⁰

Study Design: Prospective, case-control, observational study

Study Funding: Beilinson Teratology Information Service (BELTIS), a free call-in center for queries regarding drug use during pregnancy and lactation. **Patients:** There were 163 women who contacted BELTIS; however, only 137 women were available for follow-up. Most women were treated during the first trimester: 87 women had not received treatment or consultation and were offered combination treatment; 29 were treated with pyridoxine/doxylamine; 21 were offered other drug regimens; and 37 were not pharmacologically treated. There were 49 women who had prior knowledge of treatment and had either started metoclopramide therapy or wanted noncombination therapy.

Intervention: Standard recommendations first included dietary changes (small, frequent meals); if vomiting continued, pyridoxine 50 mg twice daily was started. If vomiting persisted, the addition of an initial dose of doxylamine 25 mg was recommended once daily in the evening. Two additional doses of 12.5 mg were recommended if required. If symptoms continued, a third-line recommendation of metoclopramide was added. If symptom control was not achieved, additional antiemetic medications and/or fluid replacement were recommended. Women were subsequently contacted up to 2 years following the initial phone conversation to report severity of nausea and vomiting, efficacy of treatment, duration of treatment, fetal growth, mode of delivery, gestational age at delivery, birth weight, gender, congenital birth defects, and infant age and development.

Results:

Primary Endpoint(s):

- Achieved symptom control was similar between treatment groups, 20/29 (69%) in the pyridoxine/doxylamine-treatment group versus 18/25 (72%) in the metoclopramide-treatment group ($P = .65$), despite more patients reporting moderate to severe symptoms in the pyridoxine/doxylamine-treatment group (28/29 [97%]) compared with the metoclopramide-treatment group (18/26 [69%]) ($P = .01$) at baseline.
- Higher rate of late preterm delivery (18% vs 0%) was observed in the pyridoxine/doxylamine-treatment group ($P = .03$).
- No significant difference between the treatment groups was observed with respect to delivery, birth weight, and spontaneous first-trimester abortions.

Comments: The daily combination regimen for the majority of patients included a daily dose of pyridoxine 100 mg and doxylamine 25 to 37.5 mg using individual products instead of the daily dose of pyridoxine 30 to 40 mg and doxylamine 30 to 40 mg found in the approved delayed-release formulation.

Limitations: Limitations included the small sample size, choice of treatment not randomized, and choice of treatment determined by the patient. With a 2-year follow-up after the treatment period, there is a significant risk of discrepancy in recollection of events that may have occurred during the pregnancy.

Drug: Delayed-Release Pyridoxine/Doxylamine vs Placebo

Reference: Koren G, et al, 2010⁵

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Duchesnay Inc.

Patients: Included 280 pregnant women, 18 years and older, in the gestational age range of 7 to 14 weeks, who had nausea and vomiting during pregnancy and a pregnancy unique quantification of emesis (PUQE) score of 6 and higher. All patients were required to be nonresponsive to conservative management, defined by the ACOG practice bulletin, including dietary/lifestyle changes.

Intervention: The recommended initial dose on day 1 of *Diclectin* (delayed-release doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) or matching placebo was 2 tablets orally at bedtime. If the nausea and vomiting were adequately controlled, this dose was continued. If the symptoms persisted into the afternoon of day 2 (defined as PUQE score of greater than 3), the patient was directed to take the usual dose of 2 tablets at bedtime and another 3 tablets starting on day 3 (1 tablet in the morning and 2 tablets at bedtime). If symptoms were inadequately controlled, the dose was increased to 4 tablets on day 4 and continued (1 tablet in the morning, 1 tablet mid afternoon, and 2 tablets at bedtime).

Results:

Primary Endpoint(s):

- Greater improvement in nausea and vomiting symptoms was observed in the *Diclectin*-treatment group compared with placebo, -4.8 ± 2.7 PUQE vs -3.9 ± 2.6 , respectively ($P = .006$).
- Greater improvement in global assessment of well-being score in the *Diclectin*-treatment group compared with placebo, -2.8 ± 2.8 vs -1.8 ± 2.2 , respectively ($P = .005$).

Secondary Endpoint(s):

- Day-by-day AUC for change in PUQE score from baseline was larger in the *Diclectin*-treatment group (61.5 ± 36.9) versus the placebo-treatment group (53.5 ± 37.5) ($P < .001$).
- A trend of more time lost from employment was observed in the placebo-treatment group compared with the *Diclectin*-treatment group.

Comments: The planned secondary analysis found no correlation between adherence and patient age or gestational age. Overall adherence was calculated by counting the number of tablets remaining at day 14 and comparing it to the number of tablets that were prescribed. Medication adherence rates were similar between the treatment arms (doxylamine/pyridoxine 90% vs placebo 86.5%; $P = .08$). However, the average number of tablets administered per day and gravidity negatively associated adherence.¹¹

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Contraindications to doxylamine/pyridoxine include hypersensitivity to doxylamine succinate, other ethanamine-derived antihistamines, pyridoxine hydrochloride, or any inactive ingredient (eg, ammonium hydroxide, n-butanol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red #27, denatured alcohol, FD&C Blue #2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 400, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, talc, titanium dioxide) in the formulation or if the patient is receiving monoamine oxidase inhibitors (MAOIs).¹

Warnings and Precautions

Doxylamine/pyridoxine is not recommended for use in woman receiving central nervous system (CNS) depressants, including alcohol. Concurrent use of these drugs can increase the risk of somnolence and severe drowsiness. The patient should not engage in activities that require complete mental alertness, such as driving or operating heavy machinery, and may be at risk of falls or accidents. The product labeling states that these activities should be avoided until the patient is cleared by their health care provider.¹

The anticholinergic properties of doxylamine succinate may cause problems in patients with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction.¹

Doxylamine/pyridoxine is classified as Pregnancy Category A; there is no increased risk of teratogenicity when used during pregnancy. Numerous cohort and case control studies, as well as meta-analyses, have concluded that doxylamine/pyridoxine is safe for use during pregnancy and is not associated with an increased risk of teratogenicity.¹

Breast-feeding is not recommended if the patient requires continued treatment with doxylamine/pyridoxine. Pyridoxine is excreted into breast milk, and doxylamine is likely excreted into breast milk. Breast-feeding infants of mothers treated with doxylamine succinate have experienced excitement, irritability, and sedation. In addition, infants with apnea or other respiratory syndromes may be vulnerable to the sedative effects of doxylamine, which may worsen their apnea or respiratory condition.¹

The safety and effectiveness of doxylamine/pyridoxine in children younger than 18 years have not been established.¹

ADVERSE REACTIONS

The most common adverse reaction reported with doxylamine/pyridoxine was somnolence.¹ Somnolence occurred in 14.3% of the patients treated with doxylamine/pyridoxine compared with 11.7% with placebo in a 15-day placebo-controlled study. No other adverse reactions in this study had an incidence of greater than 5% and were higher than in the placebo-treated group.

Possible adverse reactions that may occur with doxylamine/pyridoxine include dyspnea, palpitations, tachycardia, vertigo, vision blurred, visual disturbances, abdominal distension, abdominal pain, constipation, diarrhea, chest discomfort, fatigue, irritability, malaise, hypersensitivity, dizziness, headache, migraines, paresthesia, psychomotor hyperactivity, anxiety, disorientation, insomnia, nightmares, dysuria, urinary retention, hyperhidrosis, pruritus, rash, and maculopapular rash.¹

The risk of a fall or other accident may be included when doxylamine/pyridoxine is combined with CNS depressants (eg, alcohol).¹

DRUG INTERACTIONS

Concurrent use with an MAOI is contraindicated. If doxylamine/pyridoxine is used with an MAOI, the patient may experience prolonged and intensified anticholinergic effects from doxylamine.¹

Concurrent use with alcohol or other CNS depressants (eg, hypnotic sedatives, tranquilizers) is not recommended.¹

Concurrent use with other anticholinergic medications is not addressed in the product labeling, but

there is an additive effect when 2 or more drugs with anticholinergic activity are used together.

Administration with food may delay the onset of action and reduce the absorption of the drugs from the delayed-release tablet. Therefore, administration with food should be avoided. Instead, the drug should only be taken on an empty stomach with a glass of water.¹

RECOMMENDED MONITORING

Prior to the initiation of therapy, patients should be appropriately assessed with differential diagnosis for the clinical presentation of nausea and vomiting. The physical assessment should include laboratory tests including blood urea nitrogen, electrolytes, renal function, and liver function. Additional monitoring will include the frequency and severity of nausea and vomiting and assessment of the need for continued therapy during the progression of pregnancy.

DOSING

The recommended initial dose is 2 tablets orally at bedtime (day 1). If nausea and vomiting are adequately controlled, this dose should be continued. If nausea and vomiting persist into the afternoon of day 2, the usual dose of 2 tablets at bedtime that night and another 3 tablets starting on day 3 (1 tablet in the morning and 2 tablets at bedtime) is recommended. If the 3-tablet dose provides adequate control of symptoms on day 4, it should be continued. If inadequately controlled, the dose should be increased to 4 tablets on day 4 and continued (1 tablet in the morning, 1 tablet mid afternoon, and 2 tablets at bedtime).¹ *Diclegis* should not be used on an as-needed basis; instead, it should be used daily. The need for continued therapy should be reassessed throughout the pregnancy.¹

The maximum recommended dose is 4 tablets daily.¹

The tablets should be swallowed whole and taken on an empty stomach with a glass of water. The tablets should not be crushed, chewed, or split.¹

PRODUCT AVAILABILITY

Diclegis was approved for marketing in the United States on April 8, 2013.¹² It is available as a delayed-release tablet containing doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg in bottles of 100 tablets.¹

The product should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). The bottle should be kept tightly closed and protected from moisture. The desiccant canister should not be removed.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for *Diclegis* therapy.

CONCLUSION

Diclegis (doxylamine and pyridoxine) delayed-release tablets are approved for the treatment of nausea and vomiting during pregnancy based on a favorable efficacy and safety profile. Doxylamine and pyridoxine have been recommended as a first-line pharmacotherapeutic choice by the ACOG guidelines for at least the past 9 years.

REFERENCES

1. *Diclegis* [package insert]. Bryn Mawr, PA: Duchesnay Inc; April 2013.
2. Kutcher JS, Engle A, Firth J, Lamm SH. *Bendectin* and birth defects. II: Ecological analysis. *Birth Defects Res A Clin Mol Teratol*. 2003;67(2):88-97.
3. Brody JE. Shadow of doubt wipes out *Bendectin*. *The New York Times*. <http://www.nytimes.com/1983/06/19/weekinreview/shadow-of-doubt-wipes-out-bendectin.html?pagewanted=print>. Published June 19, 1983. Accessed May 2, 2013.
4. Clark SM, Costantine MM, Hankins GD. Review of NVP and HG and early pharmacotherapeutic intervention. *Obstet Gynecol Int*. 2012;2012:252676. doi: 10.1155/2012/252676.
5. Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: A randomized placebo controlled trial. *Am J Obstet Gynecol*. 2010;203(6):571.e1-7.
6. American College of Obstetrics and Gynecology. ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: Nausea and vomiting of pregnancy. *Obstet Gynecol*. 2004;103(4):803.
7. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med*. 2010;363(16):1544-1550.
8. Gill SK, Garcia-Bournissen F, Koren G. Systemic bioavailability and pharmacokinetics of the doxylamine-pyridoxine delayed-release combination (*Diclectin*). *Ther Drug Monit*. 2011;33(1):115-119.
9. Matok I, Clark S, Caritis S, et al. Comparing the pharmacokinetics of doxylamine/pyridoxine delayed-release combination in nonpregnant women of reproductive age and women in the first trimester of pregnancy [published online ahead of print May 1, 2012]. *J Clin Pharmacol*.
10. Ashkenazi-Hoffnung L, Merlob P, Stahl B, Klinger G. Evaluation of the efficacy and safety of bi-daily combination therapy with pyridoxine and doxylamine for nausea and vomiting of pregnancy. *Isr Med Assoc J*. 2013;15(1):23-26.
11. Costantine MM, Matok I, Chiossi G, et al. Determinants of adherence to delayed-release doxylamine and pyridoxine in patients with nausea and vomiting of pregnancy. *Ther Drug Monit*. 2012;34(5):569-573.
12. Joffe HV. NDA approval letter: *Diclegis* (doxylamine succinate and pyridoxine hydrochloride delayed-release tablets NDA 021876). US Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2013/021876Orig1s000ltr.pdf. Published April 8, 2013. Accessed April 29, 2013. ■

Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of doxylamine succinate and pyridoxine hydrochloride for the treatment of nausea and vomiting in pregnant women.

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of doxylamine succinate and pyridoxine hydrochloride.
2. Discuss the risks associated with the use of doxylamine succinate and pyridoxine hydrochloride.
3. Discuss the potential benefit of doxylamine succinate and pyridoxine hydrochloride for an individual patient.
4. Apply the information on the use of doxylamine succinate and pyridoxine hydrochloride to a case study.

Key Words—nausea, new drugs, pregnancy, vomiting

1. The US Food and Drug Administration (FDA)–approved indication for doxylamine succinate and pyridoxine hydrochloride delayed-release tablets is the:
 - a. Prevention of nausea and vomiting in pregnancy.
 - b. Treatment of hyperemesis gravidarum.
 - c. Treatment of nausea and vomiting in pregnancy in women who have not responded to conservative management.
 - d. Treatment of postoperative nausea and vomiting.
2. Doxylamine succinate is:
 - a. An antidopaminergic.
 - b. An antihistamine.
 - c. A phenothiazine.
 - d. A serotonin 5-HT₃ receptor antagonist.
3. Pyridoxine is:
 - a. Vitamin B1.
 - b. Vitamin B2.
 - c. Vitamin B6.
 - d. Vitamin B12.
4. Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are classified in Pregnancy Category:
 - a. A.
 - b. B.
 - c. D.
 - d. X.
5. Which of the following is recommended in the American College of Obstetrics and Gynecology guidelines as a first-line pharmacologic treatment of nausea and vomiting associated with pregnancy?
 - a. Metoclopramide
 - b. Ondansetron
 - c. Prochlorperazine
 - d. Pyridoxine plus doxylamine
6. Following administration of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets, peak doxylamine concentrations are reached within:
 - a. 1 hour.
 - b. 2 hours.
 - c. 5.5 hours.
 - d. 7.5 hours.
7. Administration of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets with food:
 - a. Delays the onset of action and reduces absorption.
 - b. Reduces the onset of action and increases absorption.
 - c. Reduces the onset of action and reduces absorption.
 - d. Speeds its transit through the gastrointestinal tract resulting in reduced absorption.

8. Which of the following is a contraindication to the use of doxylamine succinate and pyridoxine hydrochloride?
- a. Concomitant therapy with a monoamine oxidase inhibitor
 - c. Epilepsy
 - d. Gastrointestinal obstruction
 - b. Hypersensitivity to phenothiazines
12. Which of the following statements is true?
- a. K.S. can crush the tablets if she has trouble swallowing due to nausea or retching.
 - b. K.S. should be instructed to take the tablets with food.
 - c. K.S. should be advised that drowsiness is a common side effect and she should not drive until cleared by her health care provider.
 - d. K.S. should be advised that she will need to take this medication throughout her pregnancy.

Case History

K.S. is a 28-year-old primigravida in her 13th week. She has experienced moderate nausea and vomiting of pregnancy, with symptoms most severe in the morning but occurring intermittently throughout the day since week 6. She has tried dietary modifications, trigger avoidance, ginger, acupressure, and pyridoxine with inadequate response. She is frustrated by the resulting weight loss and the interference of her symptoms with her ability to work. K.S. and her physician have discussed treatment options and decided to initiate therapy with doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

9. What is the recommended initial dose of doxylamine succinate and pyridoxine hydrochloride for K.S.?
- a. 1 tablet orally in the morning
 - b. 1 tablet orally at bedtime
 - c. 2 tablets orally in the morning
 - d. 2 tablets orally at bedtime
10. Symptoms persisted in K.S. following administration of the first dose. What dose should be subsequently recommended for K.S.?
- a. 1 tablet in the morning and 1 tablet at bedtime
 - b. 1 tablet in the morning and 2 tablets at bedtime
 - c. 2 tablets in the morning and 1 tablet at bedtime
 - d. 1 tablet in the morning, 1 tablet at noon, and 1 tablet at bedtime
11. The maximum recommended dose is:
- a. 2 tablets daily.
 - b. 3 tablets daily.
 - c. 4 tablets daily.
 - d. 5 tablets daily.
13. The most common adverse event associated with doxylamine succinate and pyridoxine hydrochloride delayed-release tablets was:
- a. Constipation.
 - b. Dry mouth.
 - c. Headache.
 - d. Somnolence.
14. K.S. calls you after her mom told her not to take this product because it caused birth defects and had been taken off the market. Which of the following is the most accurate response?
- a. Although a product with these ingredients was discontinued after a number of lawsuits alleged the product caused birth defects, no increased incidence of birth defects was observed with the combination.
 - b. The product has been completely reformulated and these new ingredients are not associated with birth defects.
 - c. There is an increased risk of birth defects with the use of this product, but it is the only treatment available.
 - d. The product actually reduces the risk of birth defects.
15. Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets should be used with caution in patients with:
- a. Asthma.
 - b. Increased intraocular pressure.
 - c. Urinary obstruction.
 - d. All of the above.

This CE activity is co-sponsored by ProCE, Inc. and *Hospital Pharmacy*. ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-13-069-H01-P has been assigned to this knowledge-based home-study CE activity (initial release date 10-01-13). This CE activity is approved for 1.5 contact hours (0.15 CEUs) in states that recognize ACPE providers. This CE activity is provided at no cost to participants. Statements of credit will be issued online upon completion of the evaluation and the post-test with a score of 70% or higher. No partial credit will be given.

Release Date: October 1, 2013

Expiration Date: October 1, 2015

Continuing Education for this activity is processed through the ProCE online CE Center. To receive CE credit, please go to:

- www.ProCE.com/HPJFDR
- Click to access the activity page to enroll and complete the Post-Test and Evaluation

With a passing grade of 70% or greater on the Post-Test, you will be able to print your CE statement of credit online.

For questions related to registering for and obtaining CE credit, contact ProCE at 630-540-2848 or Info@ProCE.com.