

**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:** dru069

**Topic:** Anzemet<sup>®</sup>, dolasetron

**Date of Origin:** September 2001

**Revised/Effective Date:** November 14, 2008

**Next Review Date:** November 2009

**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**

Dolasetron (Anzemet<sup>®</sup>) is a 5-HT<sub>3</sub> antagonist medication used to prevent nausea and vomiting.

## Policy/Criteria

- I. Most contracts require prior authorization approval of oral dolasetron prior to coverage. Oral dolasetron may be considered medically necessary when both criteria A and B below are met.
  - A. Oral dolasetron is used for the prevention and/or treatment of nausea/vomiting associated with chemotherapy and/or radiation therapy; or prevention of post-operative nausea and vomiting (PONV).

### AND

- B. Treatment with at least one generic 5-HT<sub>3</sub> antagonist (ondansetron or granisetron) is not effective or not tolerated.

## II. Administration, Quantity Limitations, and Authorization Period

- A. Regence considers oral dolasetron to be a self-administered medication.
- B. When prior authorization is approved, oral dolasetron may be authorized in quantities of up to four tablets per month. Quantities exceeding four tablets per month may be approved when appropriate for the prescribed chemotherapy and/or radiation treatment regimen, not to exceed 30 tablets per month (for example, if chemotherapy is given on an every 3-week cycle, two tablets per month may be authorized, or if radiation therapy is scheduled three times per week, twelve tablets per month may be authorized).
- 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.

## III. Oral dolasetron is considered investigational when used for all other conditions, including but not limited to:

- A. Hyperemesis gravidarum.
- B. Nausea and vomiting of pregnancy (NVP).

## Position Statement

- All of the 5-HT<sub>3</sub>-antagonist antiemetic medications are effective in preventing nausea and vomiting. [24-26, 30]
- No single 5-HT<sub>3</sub>-antagonist antiemetic medication has been shown to work better or be better tolerated than another when given in equally potent doses whether given by mouth, by injection, or via a topical patch. [12, 31-36]
- Two of the 5-HT<sub>3</sub>-antagonist antiemetic medications, ondansetron and granisetron, are available as generics and provide the best value in preventing nausea and vomiting.

## *Chemotherapy and Radiation Therapy*

- The American Society of Clinical Oncology (ASCO) provides recommendations for antiemetic use during chemotherapy: [12]
  - \* Acute Emesis (0 - 24 hours after chemotherapy) - A single dose of a 5-HT<sub>3</sub> receptor antagonist just prior to highly emetogenic chemotherapy agents (e.g., cisplatin, cyclophosphamide, and lomustine) and moderately emetogenic chemotherapy (e.g., carboplatin, iphosphamide, and idarubicin) as part of an antiemetic regimen.
  - \* For consecutive days of highly and moderately emetogenic chemotherapy, a 5-HT<sub>3</sub> receptor antagonist during each day of chemotherapy.
  - \* Delayed Emesis (24 to 72 hours after chemotherapy) - For moderately emetogenic chemotherapy, dexamethasone or a 5-HT<sub>3</sub> receptor antagonist is recommended for up to two to three days. Treatment with 5-HT<sub>3</sub> receptor antagonists is no longer recommended for delayed emesis due to highly emetogenic chemotherapy.
  - \* An antiemetic, including a 5-HT<sub>3</sub> receptor antagonist, may be considered in high dose or pediatric chemotherapy.
- ASCO provides recommendations for antiemetic use during radiation therapy:
  - \* A single dose of a 5-HT<sub>3</sub> antagonist before each fraction of radiation when there is high, intermediate, or low risk of radiation-induced emesis.

- \* A dopamine receptor or a 5-HT<sub>3</sub> antagonist as needed for minimal-risk radiation therapy.
- There are no well-designed studies to support antiemetic therapy for periods greater than 24 hours after the last dose of radiation therapy.
- A small (n = 39) double-blind, randomized parallel study evaluated the efficacy of 1 mg granisetron IV vs. 3 mg IV. Of the group getting 3 mg, 90% showed complete response vs. 60% in the group receiving 1 mg. The approved U.S. dose of 2 mg was not evaluated.<sup>[27]</sup>

*Nausea and Vomiting of Pregnancy (NVP) versus Hyperemesis Gravidarum*

- NVP occurs in the majority of pregnant women, is commonly limited in duration, and does not adversely affect pregnancy outcomes.
  - \* Non-pharmacological treatment of NVP is preferred over pharmacological therapies and includes dietary modifications; eating small, bland, frequent, low fat, high carbohydrate meals; avoiding emetogenic odors; avoiding iron supplements; and relaxation.
  - \* Hyperemesis gravidarum, which is more rare than uncomplicated NVP, is severe, persistent, uncontrollable nausea and vomiting during pregnancy resulting in dehydration and weight loss. Electrolyte and metabolic disturbances, nutritional deficiency, and ketosis may also occur.
  - \* Treatment of hyperemesis gravidarum may include non-pharmacological therapies and parenteral hydration with glucose, electrolytes, and vitamins, often in an inpatient setting. Antiemetics, corticosteroids, and sedatives are used for the acute vomiting.

## *Antiemetics in Pregnancy and Hyperemesis Gravidarum*

- Diphenhydramine, dimenhydrinate, meclizine, doxylamine, and metoclopramide (rated FDA Pregnancy category B) have not been associated with an increased risk of teratogenicity when used in humans, and have demonstrated some level of efficacy in NVP or hyperemesis gravidarum in clinical trials.
- There is extensive experience indicating that the combination of doxylamine and pyridoxine is safe in pregnancy. Doxylamine and pyridoxine are available as Diclectin<sup>®</sup> in Canada. Canadian physicians use this product as first line therapy for NVP. Doxylamine and pyridoxine are currently available without a prescription in the U.S.
- Ondansetron, granisetron, and dolasetron are also rated FDA Pregnancy category B. [24-26] Studies using ondansetron during pregnancy are limited and there are currently no clinical trials evaluating dolasetron or granisetron in NVP or hyperemesis gravidarum.
- Ondansetron has not demonstrated superiority over other antiemetics in the treatment of hyperemesis gravidarum. There are no controlled trials that evaluate the safety of high-dose or long-term use of ondansetron in pregnancy.
- Doses of ondansetron used in clinical trials for the treatment of hyperemesis gravidarum ranged from 4mg to 10mg IV daily, up to TID. [6, 15-16]
- Ondansetron may be considered medically necessary for the treatment of hyperemesis gravidarum. There is no useful evidence supporting the use of dolasetron or granisetron for this indication.

## *Postoperative Nausea and Vomiting*

- Efficacy and benefits in preventing/treating postoperative nausea and vomiting with a 5-HT<sub>3</sub> antagonist have not been demonstrated beyond 24 hours.

## Safety

- Headache was the most commonly observed adverse effect with 5-HT<sub>3</sub> receptor antagonists in clinical trials. <sup>[24-26]</sup>

### *5-HT<sub>3</sub> receptor antagonists: Use in Other Conditions*

- There are preliminary trials which have used ondansetron in the treatment of memory impairment in schizophrenic patients <sup>[17]</sup>, neuropathic pain <sup>[18]</sup>, pruritus of cholestasis <sup>[19]</sup>, ataxia and incoordination secondary to brain injury <sup>[20]</sup>, Tourette's disorder <sup>[21]</sup>, fatigue with primary biliary cirrhosis <sup>[22]</sup>, fatigue in chronic Hepatitis C, <sup>[23]</sup> cocaine dependence <sup>[28]</sup> and schizophrenia <sup>[29]</sup>. The trials were all of short duration, they enrolled small populations, and several included ondansetron given by injection.

## References

1. Broussard CN, Richter, JE. "Nausea and vomiting of pregnancy." *Gastroenterol Clin North Am.* 1998;27(1):123-51.
2. Cunningham FG, et al: *Williams Obstetrics*, 21st Ed. San Francisco, McGraw Hill, 1997.
3. Murphy PA. "Alternative therapies for nausea and vomiting of pregnancy." *Obstetrics and Gynecol.* 1998;91(1):149-55.
4. Beers MH, Berkow R. *The Merck Manual of Diagnosis and Therapy, 17th Ed.* Merck Research Laboratories, New Jersey, 1999.
5. Tierney LM, McPhee SJ, Papadakis MA. *Current Medical Diagnosis & Treatment, 40th Ed.* McGraw Hill, San Francisco, 2001.
6. Sullivan CA, et al. "A pilot study of intravenous ondansetron for hyperemesis gravidarum." *Am J Obstet Gynecol.* 1996;174(5):1565-8.

7. Atanackovic G, et al. The safety of higher than standard dose of doxylamine-pyridoxine (Diclectin) for nausea and vomiting of pregnancy. *J Clin Pharmacol.* 2001;41(8):842-5.
8. Briggs GG, Freeman RK, Yaffee SJ: *Drugs in Pregnancy and Lactation, 5th ed.* Baltimore, Lippincott Williams & Wilkins 1998, New York.
9. Jewell D, Young G. "Interventions for nausea and vomiting in early pregnancy." *Cochrane Database Syst Rev.* 2000;(2):CD000145.
10. Leathem AM. "Safety and efficacy of antiemetics used to treat nausea and vomiting in pregnancy." *Clin Pharm.* 1986;5(8):660-8.
11. Nageotte MP, et al. "Droperidol and diphenhydramine in the management of hyperemesis gravidarum." *Am J Obstet Gynecol.* 1996;174(6):1801-5.
12. American Society of Clinical Oncology; Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, et. al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol.* 2006 Jun 20;24(18):2932-47.
13. Gora-Harper ML, et al. "ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery." *Am J Health Sys Pharm.* 199;56(8):730-64.
14. Tincello DG, Johnstone MJ. "Treatment of hyperemesis gravidarum with the 5-HT<sub>3</sub> antagonist ondansetron (Zofran)." *Postgrad Med J.* 1996;72:688-9.
15. World MJ. "Ondansetron and hyperemesis gravidarum." *Lancet.* 1993;341:185.
16. Guikontes E, Spantideas A, Diakakis J. "Ondansetron and hyperemesis gravidarum." *Lancet.* 1992;340:1223.
17. Levkovitz Y, Arnest G, Mendlovic S, et al. "The effect of ondansetron on memory in schizophrenic patients." *Brain Res Bull.* 2005;65(4):291-5.
18. McCleane GJ, Suzuki R, Dicenson AH. "Does a single intravenous injection of the 5-HT<sub>3</sub> receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study." *Anesth Analg.* 2003;97:1474-8.

19. O'Donohue JW, Pereira SP, Ashdown AC, et al. "A controlled trial of ondansetron in the pruritus of cholestasis." *Aliment Pharmacol Ther.* 2005;21(8):1041-5.
20. Madelcorn J, Cullen NK, Bayley MT. "A preliminary study of the efficacy of ondansetron in the treatment of ataxia, poor balance and incoordination from brain injury." *Brain Inj.* 2004;18(10):1025-39.
21. Toren P, Weizman A, Ratner S, et al. "Ondansetron treatment in Tourette's disorder: a 3-week, randomized, double-blind, placebo-controlled study." *J Clin Psychiatry.* 2005;66:499-503.
22. Theal JJ, Toosi MN, Girlan L, et al. "A randomized, controlled crossover trial of ondansetron in patients with primary biliary cirrhosis and fatigue." *Hepatology.* 2005;41(6):1305-12.
23. Piche T, Vanbiervliet G, Cherikh F, et al. "Effect of ondansetron, a 5-HT<sub>3</sub> receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double-blind, placebo controlled study." *Gut.* 2005;54:1169-73.
24. Anzemet<sup>®</sup> (dolasetron) prescribing information. Aventis Pharmaceuticals, Inc.; Kansas City, MO; June 2006.
25. Kytril<sup>®</sup> (granisetron) prescribing information. Roche Laboratories, Inc; Nutley, NJ; November 2005.
26. Zofran<sup>®</sup> (ondansetron) prescribing information. GlaxoSmithKline; Research Triangle Park, NC; February 2006.
27. Kurnianda J, Hisyam B, Wahyuningsih E, Hutajulu SH. The efficacy of granisetron for cancer patients undergoing platinum-based chemotherapy: comparison of 1 milligram versus 3 milligram doses in preventing nausea and vomiting. *Acta Med Indones.* 2005 Oct-Dec;37(4):210-3.
28. Johnson BA, Roache JD, Ait-Daoud N, Javors MA, Harrison JM, Elkashef A, et. al. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence. *Drug Alcohol Depend.* 2006 Oct 1;84(3):256-63.

29. Zhang ZJ, Kang WH, Li Q, Wang XY, Yao SM, Ma AQ. Beneficial effects of ondansetron as an adjunct to haloperidol for chronic, treatment-resistant schizophrenia: a double-blind, randomized, placebo-controlled study. *Schizophr Res.* 2006 Dec;88(1-3):102-10.
30. Aloxi<sup>®</sup> (palonosetron) prescribing information. Eisai, Inc.; Woodcliff Lake, NJ; August 2008.
31. Sancuso<sup>®</sup> (granisetron transdermal system) prescribing information. ProStrakan, Inc.: Bedminster, NJ; August 2008.
32. Peterson K, McDonagh MS, Carson S, Lopez S. Drug Class Review on Newer Antiemetics. Oregon Health Sciences University (OHSU) Evidenced-Based Practice Center Final Report; 2006.
33. Centre for Reviews and Dissemination. Use of 5-HT<sub>3</sub>-receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. Database of Abstracts of Reviews of Effects (DARE) ©2008. Available at: <http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=12003008193>. Accessed on 10/14/2008.
34. Jordan K, Hinke A, Grothey A, Voigt W, Arnold D, et al. A meta-analysis comparing the efficacy of four 5-HT<sub>3</sub>-receptor antagonists for acute chemotherapy-induced emesis. *Support Cancer Care.* 2007;15:1023-33.
35. Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann Oncol.* 2006;17(9):1441-9.
36. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™: Antiemesis v.3.2008. Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf). Accessed on 10/14/08.

<b>Cross References</b>
Aloxi <sup>®</sup> , palonosetron dru163
Emend <sup>®</sup> , aprepitant dru091
Kytril <sup>®</sup> , granisetron dru068
Sancuso <sup>®</sup> , granisetron topical patch dru164
Zofran <sup>®</sup> , ondansetron dru046

<b>Codes</b>	<b>Number</b>	<b>Description</b>
N/A		