

**Regence BlueCross BlueShield of Oregon • Regence BlueShield  
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**Medication Policy Manual**

**Policy No:** dru068

**Topic:** Kytril<sup>®</sup>, granisetron

**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**

Granisetron (Kytril<sup>®</sup>) is a 5-HT<sub>3</sub> antagonist medication used to prevent nausea and vomiting. It is available both as generic granisetron and as brand name Kytril.

## Policy/Criteria

- I. Most contracts require prior authorization approval of oral granisetron prior to coverage of quantities greater than 8 tablets or 30 mL of solution per month. Oral granisetron in quantities up to 8 tablets or 30 mL per month may be considered medically necessary and may be covered without authorization.
  
- II. Granisetron in quantities exceeding 8 tablets or 30 mL per month may be considered medically necessary when either criterion A or B below is met:
  - A. **Chemotherapy/radiation therapy:** Granisetron in quantities exceeding 8 tablets or 30 mL per month may be considered medically necessary for the prevention and/or treatment of nausea/vomiting associated with chemotherapy and/or radiation therapy.

**OR**

- B. **Other severe nausea and vomiting** when both criteria 1 and 2 below are met:
  1. Physician's assessment of patient's current status and goals of treatment are documented in medical information.

**AND**

2. Nausea and vomiting despite treatment with at least three generic antiemetic agents, including, but not limited to, ondansetron, metoclopramide, prochlorperazine and promethazine.

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

- A. Regence considers oral granisetron to be a self-administered medication.
  
- B. When prior authorization is approved, oral granisetron may be authorized in quantities consistent with the treatment plan (e.g., prescribed chemotherapy regimen). Quantities exceeding 60 tablets or 300 mL per month are considered investigational.
  
- C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

## 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. 5-HT<sub>3</sub> receptor antagonists are 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 granisetron 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 to treat 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. [24-26]

### 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.

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<b>Cross References</b>		
Aloxi <sup>®</sup> , palonosetron dru163		
Anzemet <sup>®</sup> , dolasetron dru069		
Emend <sup>®</sup> , aprepitant dru091		
Sancuso <sup>®</sup> , granisetron topical patch dru164		
Zofran <sup>®</sup> , ondansetron dru046		

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