



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Antiemetics - Oral and Topical
Serotonin-3 Receptor
Antagonists**

**Effective Date 2/15/2010
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Coverage Policy Number 4023**

Table of Contents

Coverage Policy	1
General Background	4
Coding/Billing Information	7
References	7
Policy History	13

Hyperlink to Related Coverage Positions

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

Consistent with the Food and Drug Administration (FDA) approved manufacturer product information and frequency of chemotherapy or radiation treatment cycles, CIGNA covers the following quantities of **ORAL** therapy without prior authorization:

- **Dolasetron (Anzemet®) ORAL only**
5 tablets covered without prior authorization
- **Granisetron (Kytril®) ORAL only**
10 tablets covered without prior authorization
- **Ondansetron (Zofran®, Zofran ODT®) ORAL only**
24 tablets covered without prior authorization
2 bottles of oral solution covered without prior authorization
- **Ondansetron 24mg strength ORAL only**
5 tablets covered without prior authorization

Consistent with FDA approved manufacturer product information and frequency of chemotherapy CIGNA covers granisetron (Sancuso®) patch as medically necessary for the following quantity:

- Granisetron (Sancuso®) - 4 topical patches per 30 days

CIGNA covers additional quantities of oral serotonin-3 receptor antagonist antiemetic therapy when ANY of the following medical necessity criteria is met:

- For Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV), both acute and delayed, when cancer chemotherapy regimen schedule necessitates more frequent administration or dosage adjustment than initial quantities allow
- For Prevention of Radiotherapy-Induced Nausea and Vomiting (RINV) when radiotherapy regimen schedule necessitates more frequent administration or dosage adjustment than initial quantities allow
- For Treatment or Prevention of Postoperative Nausea and Vomiting (PONV) when surgery schedules necessitate more frequent administration or dosage adjustment than initial quantities allow
- For Treatment of Pregnancy related nausea and vomiting
- For Treatment or Prevention of ESTABLISHED Nausea and Vomiting when BOTH of the following conditions are met:
 - when the use relates to chemotherapy, surgery, uremia or AIDS
 - when there has been a failure, contraindication or intolerance to at least ONE other first-line nausea and vomiting therapy [antihistamines, butyrophenones, corticosteroids (generally not in first trimester), metoclopramide, or phenothiazines]

Oral and topical serotonin-3 receptor antagonist antiemetic therapy includes the following drugs:

- **Generic:**
 - granisetron
 - ondansetron
- **Non-Preferred Brand:**
 - dolasetron (**Anzemet**[®])
 - granisetron (**Kytril**[®], **Sancuso**[®])
 - ondansetron (**Zofran**[®], **Zofran ODT**[®])

FDA Approved Indications / Dosing Recommendations:

Drug	FDA-Approved Indications	Dosing Recommendation
dolasetron (Anzemet [®])	-Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses -Prevention of postoperative nausea and vomiting	<u>Prevention of CINV</u> Adult: 100 mg once daily within one hour before chemotherapy Pediatrics: 1.8 mg/kg given within one hour before chemotherapy, up to a maximum of 100 mg <u>Prevention of PONV</u> Adults: 100 mg within two hours before surgery Pediatrics: 1.2 mg/kg given within two hours before surgery, up to a maximum of 100 mg
granisetron (Kytril [®])	-Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin -Prevention of nausea and vomiting associated	<u>Emetogenic Chemotherapy</u> 2 mg once daily or 1 mg twice daily <u>Radiation</u>

	with radiation, including total body irradiation and fractionated abdominal radiation	2 mg once daily
granisetron (Sancuso®)	Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days	One patch 24 hours before chemotherapy. Patch can be worn for up to 7 days.
ondansetron (Zofran®, Zofran ODT®)	<ul style="list-style-type: none"> - Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq 50 \text{ mg/m}^2$ - Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy - Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen - Prevention of postoperative nausea and/or vomiting 	<p><u>CINV with highly emetogenic chemotherapy</u> 24 mg 30 minutes before the start of single-day chemotherapy</p> <p><u>CINV with moderately emetogenic chemotherapy</u> Adults: One 8-mg tablet or ODT tablet or 10 mL oral solution given twice a day One 8-mg tablet or ODT tablet or 10 mL oral solution give twice a day for 1 to 2 days after completion of chemotherapy Pediatrics: - ≥ 12 years of age is same as adult - 4-11 years of age – 5mL of oral solution 3 times a day One 4-mg tablet or ODT tablet or 5 mL oral solution give 3 times a day for 1 to 2 days after completion of chemotherapy</p> <p><u>Prevention of RINV</u> Adults: One 8-mg tablet or ODT tablet or 10 mL oral solution given 3 times a day. Subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.</p> <p><u>Prevention of PONV</u> two 8-mg tablet or ODT tablet or 20 mL oral solution one hour before induction of anesthesia.</p>

Drug Availability

Anzemet

50 mg and 100mg tablets each supply in 5 and 10 unit dose pack

Kytril

1 mg unit of use 2's, and 1 mg single unit package 20's

Sancuso

Package of 1 patch

Zofran

4 mg tablets in daily unit dose packs of 3 tablets, bottles of 30 tablets, and unit dose packs of 100 tablets

Zofran ODT

4 mg ODT tablets in unit dose packs of 30 tablets and 8 mg ODT tablets in unit dose packs of 10 tablets and 30 tablets

Zofran Oral Solution

5mg/5 mL in 50 mL bottle

General Background

Five oral serotonin-3 (5-HT₃) receptor antagonists are approved and marketed in the United States including ondansetron (Zofran[®], Zofran ODT[®], and generic ondansetron 24 mg strength), granisetron (Kytril[®]), and dolasetron (Anzemet[®]). Granisetron transdermal system (Sancuso[®]), the first serotonin 5-HT₃ receptor antagonist available in a transdermal system, is also approved for the prevention of chemotherapy induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic chemotherapy. These agents have similar efficacy for these indications at approved doses.

Pharmacology/Pharmacokinetics

The 5-HT₃ receptor antagonists act by blocking peripheral serotonin receptors which prevents afferent vagal stimulation from the gut to the chemoreceptor trigger zone (CTZ) in the brain, a part of the brain primarily associated with nausea and vomiting. All oral 5-HT₃ receptor antagonists are well absorbed and bind 5-HT₃ receptors in the GI tract within 30 minutes of administration. Clinical trials demonstrate that these agents are equally effective with oral or intravenous (IV) administration, particularly with the higher doses used in CINV. With transdermal system, granisetron passively diffuses across intact skin. Maximum concentrations are reached approximately 48 hours after application, but time to peak can vary widely with a range from 24 to 168 hours.

Guidelines

Several organizations have published updated guidelines on the management of acute and delayed CINV, including American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), and the European Society for Medical Oncology (ESMO).

Treatment guidelines base antiemetic recommendations on the emetogenic potential of the chemotherapy being administered. Four categories of emetogenic risk were established and include: high (emetogenic risk of 90% without antiemetics), moderate (emetogenic risk of 30% to 90%), low (emetogenic risk of 10% to 30%) and minimal (emetogenic risk < 10%). Emetogenic risk is separated for both oral and intravenous chemotherapy. Appendix B categorizes the emetogenic potential of both intravenous and oral chemotherapy. For patients receiving combination chemotherapy, administer antiemetics according to the chemotherapeutic agent with the highest emetic risk.

The ASCO and MASCC 2006 updated guidelines recognize that the 5HT3 receptor antagonists are the “gold standard” for antiemetic therapy. All the new treatment guidelines recommend for highly emetogenic chemotherapy a 5-HT₃ receptor antagonist on day one plus dexamethasone and aprepitant (or fosaprepitant dimeglumine) on days 1 through 3. For moderately emetogenic chemotherapy, a 5-HT₃ receptor antagonist and dexamethasone are recommended for day one. The exception to this category is for patients receiving an anthracycline and cyclophosphamide. These patients should receive a 5-HT₃ receptor antagonist, dexamethasone, and aprepitant on day one. No antiemetic therapy is recommended for patients receiving chemotherapy with minimal emetogenic risk. Any of the available 5-HT₃ receptor antagonists can be utilized. According to the 2006 ASCO antiemetic guidelines, the 5-HT₃ receptor antagonists have equivalent safety and efficacy and can be used interchangeably when used at equivalent doses for the prevention of acute emesis. Additionally, oral formulations are equally efficacious to intravenous forms. Following are the treatment recommendations for prevention of acute nausea and vomiting in patients receiving chemotherapy.

Treatment Recommendations for Prevention of Acute Nausea and Vomiting

Chemotherapy Classification	ASCO 2006	MASCC 2008	ESMO 2008	NCCN 2007
Highly Emetogenic Chemotherapy	5-HT ₃ antagonist plus Dexamethasone plus	5-HT ₃ antagonist plus Dexamethasone plus	5-HT ₃ antagonist plus	5-HT ₃ antagonist plus Dexamethasone plus

Chemotherapy Classification	ASCO 2006	MASCC 2008	ESMO 2008	NCCN 2007
	Aprepitant	Aprepitant	Dexamethasone plus Aprepitant	Aprepitant/Fosaprepitant
Anthracycline – Cyclophosphamide Regimen	5-HT ₃ antagonist plus Dexamethasone plus Aprepitant	5-HT ₃ antagonist plus Dexamethasone plus Aprepitant	5-HT ₃ antagonist plus Dexamethasone plus Aprepitant	5-HT ₃ antagonist plus Dexamethasone plus Aprepitant/Fosaprepitant
Other Moderately Emetogenic Chemotherapy	5-HT ₃ antagonist plus Dexamethasone	5-HT ₃ antagonist plus Dexamethasone	5-HT ₃ antagonist plus Dexamethasone	5-HT ₃ antagonist plus Dexamethasone ± Lorazepam
Low Emetogenic Chemotherapy	Dexamethasone	Dexamethasone	Single agent such as Dexamethasone	Dexamethasone OR Prochlorperazine OR Metoclopramide ± Lorazepam
Minimal Emetogenic Chemotherapy	As needed Dexamethasone, Metoclopramide or Phenothiazine	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis

Treatment guidelines also provide recommendations for managing delayed CINV. For chemotherapy with high emetic risk, the combination of dexamethasone and aprepitant is recommended. The 5-HT₃ receptor antagonists are no longer recommended in combination with dexamethasone. Treatment guidelines differ in their recommendations for delayed nausea and vomiting in patients receiving moderately emetogenic chemotherapy. For other chemotherapy with moderate risk of emesis, dexamethasone or a 5-HT₃ receptor antagonist is recommended. No antiemetics are recommended for delayed CINV for patients receiving chemotherapy with low or minimal emetogenic potential. Following are the treatment recommendations for delayed nausea and vomiting in patients receiving moderately emetogenic chemotherapy.

Treatment Recommendations for Delayed Nausea and Vomiting Following Moderately Emetogenic Chemotherapy for Different Clinical Guidelines

Chemotherapy Classification	ASCO 2006	MASCC 2008	ESMO 2008	NCCN 2007
Highly Emetogenic Chemotherapy	Dexamethasone on days 2 and 3 AND Aprepitant on days 2 and 3	Dexamethasone on days 2 and 3 (± day 4) AND Aprepitant on days 2 and 3	Dexamethasone on days 2 and 3 AND Aprepitant on days 2 and 3	Dexamethasone on days 2 to 4 AND Aprepitant on days 2 and 3
Anthracycline – Cyclophosphamide Regimen (listed as moderate emetic risk)	Aprepitant on days 2 and 3	Aprepitant OR dexamethasone on days 2 and 3.	Dexamethasone or Aprepitant	Aprepitant on days 2 and 3 ± dexamethasone ± lorazepam. Aprepitant should be added for select patients receiving other chemotherapy with moderate emetic risk including carboplatin, cisplatin, epirubicin, doxorubicin, ifosfamide, irinotecan or methotrexate
Other Moderately Emetogenic Chemotherapy	Dexamethasone OR 5-HT ₃ antagonist	Dexamethasone (preferred) OR 5-HT ₃ antagonist (alternative)	Corticosteroid OR 5-HT ₃ antagonist	Dexamethasone OR 5-HT ₃ antagonist ± Lorazepam

A key finding of the ASCO consensus group is that oral 5-HT₃ receptor antagonists are recommended over the intravenous form whenever the patient is able to take oral medications with a level IA grade of evidence based on safety, efficacy, and cost. This scoring is the highest recommendable score and the best grade of evidence by the ASCO consensus group. This finding is maintained in 2006 updates to the recommendations.

Clinical Overview

The 5-HT₃ receptor antagonists are most efficacious in preventing nausea and may be beneficial in the treatment of established nausea and vomiting associated with surgery, chemotherapy, or pregnancy. The 5-HT₃ receptor antagonists are typically reserved for second-line therapy in the treatment of nausea and vomiting. They are used after the failure of common antiemetic treatments such as metoclopramide, corticosteroids, antihistamines, butyrophenones, or phenothiazines to control nausea, or they may be used in combination with these agents. They may also be considered if the side effects of more common agents are deemed intolerable by the patient.

As many patients continue to receive chemotherapy and have surgical procedures performed in an ambulatory setting, use of potent antiemetic therapies is required outside of a hospital setting. Therapy with the oral 5-HT₃ receptor antagonists ranges from one dose to several weeks of therapy. Agents in this class are rarely used for long-term management of symptoms. Serotonin-3 receptor antagonist therapy typically ends when the underlying cause of nausea and vomiting ceases to be a problem. For example, the need for an antiemetic to treat CINV ends when the course of chemotherapy ends. Duration of therapy for unlabeled uses such as pregnancy-associated nausea or uremia-induced nausea or pruritus may require chronic dosing to prevent these symptoms from recurring.

Delayed chemotherapy-induced nausea and vomiting is also called delayed emesis. It develops 24 to 72 hours after the patient receives chemotherapy, and may last for several days. This adverse effect of cancer chemotherapy typically occurs with cisplatin-based regimens, and the risk of delayed CINV increases when cisplatin-containing regimens are given over multiple days. The majority of trials evaluating 5-HT₃ antagonists for the prevention of delayed emesis are for no longer than seven days.

The 5-HT₃ receptor antagonists are rarely used for indications outside of cancer chemotherapy, radiation therapy or postoperative nausea and vomiting (FDA-approved indications). Low-cost antiemetic alternatives are typically efficacious for most causes of nausea and vomiting; therefore, the 5-HT₃ receptor antagonists are typically used as second- or third-line therapy for these patients.

According to ASCO antiemetic guidelines and available clinical studies, any of the available 5-HT₃ receptor antagonists can be utilized for prevention of acute nausea and vomiting in patients receiving chemotherapy. The 5-HT₃ receptor antagonists at equivalent doses have equivalent safety and efficacy and can be used interchangeably for acute emesis. Additionally, oral formulations are equally efficacious to intravenous forms. One unpublished trial is available evaluating the efficacy of the granisetron transdermal system compared to oral granisetron in 641 patients receiving moderately or highly emetogenic chemotherapy. Overall, outcomes were similar with the granisetron transdermal system resulting in a good outcome for 60.2% of patients and oral granisetron resulting in a good outcome for 64.8% of patients.

Approximately 50 to 90% of pregnant women experience some nausea and vomiting during pregnancy. The majority do not require antiemetic therapy and can manage symptoms with nonpharmacologic treatments. Severe nausea and vomiting that lead to dehydration, malnutrition, and hospitalization (hyperemesis gravidarum) occur in approximately 0.5 to 10 out of every 1000 pregnancies and peak during the eighth to twelfth week of pregnancy. Current American College of Obstetrician-Gynecologists (ACOG) Practice Guidelines reserve the use of ondansetron after the failure of nonpharmacologic and first-line pharmacologic therapies such as antihistamines; however, there are no adequate and controlled studies to date using ondansetron for hyperemesis gravidarum, and the drug should be used during pregnancy only when clearly needed. Ondansetron has a teratogenicity classification of B and limited data suggest safety in pregnancy.

Uremia is a symptom of end-stage renal disease (ESRD), which was diagnosed in over 300,000 Americans in 1998. By 2010, this number will likely double. Adverse effects of uremia include nausea, vomiting, metallic taste, and abdominal distension. Uremic patients often receive traditional antiemetics first, but two case reports and one trial of ondansetron suggest it may significantly reduce nausea and vomiting in the presence of uremia.

Patients with gastric stasis often experience nausea, vomiting, and abdominal bloating. Gastric stasis may be a result of gastric outlet obstruction, gastritis, irritable bowel syndrome, or it may be idiopathic. The 5-HT₃ receptor antagonists are proposed to be a possible second-line agent for the management of this disorder, since they have some effect on accelerating gastric emptying in animal models.

Adverse Reactions/Warnings

All oral 5-HT₃ antagonists have been associated with QT interval prolongation, although no cases of torsades de pointes have been reported. Insufficient data are available to determine whether the risk is greater with one agent compared to another. The safest action is to avoid using any 5-HT₃ antagonist concomitantly with agents that also prolong the QTc interval or in patients at high risk for torsades de pointes. The consensus of several national and international organizations is that these agents have similar efficacy at recommended doses. All oral and topical agents are well-tolerated with common side effects, including headache and changes in bowel frequency.

Coding/Billing Information

Note: This section is not in use.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	12/15/2008	4023	Oral Serotonin-3 receptor Antagonist Antiemetics
Great-West Healthcare	12/2005	MDL96.100.1	Anzemet
	6/2007	MDL 96.101.2	Kytril
	6/2007	MDL 96.102.2	Zofran

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.