BlueCross BlueShield of Alabama

Antiemetic Agents Quantity Limit Program Summary

This program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Antiemetic Agents Quantity Limit (QL) is to provide antiemetic therapy with the requested agent for up to 7 days of cancer chemotherapy or radiotherapy. Requests for Sancuso will be evaluated for use beyond 14 days of cancer chemotherapy. Emend 40 mg tablets, Kytril, and Zofran injection are not included in the program. The criteria will also evaluate Cesamet for additional quantities after conventional antiemetics have been shown to give an inadequate response. Requests for larger quantities of the requested agent may be approved if prescriber provides documentation indicating chemotherapy or radiation treatment extending beyond the set limit, delayed emesis to highly emetogenic chemotherapy, or hyperemesis gravidarum.

QUANTITY LIMIT TARGET AGENTS - RECOMMENDED LIMITS

Brand (generic)	GPI	Quantity Per 30 Day Limit
Akynzeo® (netupitant/palonosetron)		
300 mg / 0.5 mg	50309902290120	2 capsules
Anzemet® (dolasetron)		
50 mg tablet	50250025200320	7 tablets
100 mg tablet	50250025200330	7 tablets
Cesamet® (nabilone)		
1 mg capsule	50300040000110	42 capsules
Emend® (aprepitant)		
80 mg capsule[a]	50280020000120	4 capsules
125 mg capsule[a]	50280020000130	2 capsules
Emend Therapy Pack (1x125 mg capsule, 2x80 mg capsules)[a]	50280020006320	2 therapy packs
125mg/5mL oral suspension	50280020001930	6 single use kits
granisetron		
1 mg tablet[a]	50250035100310	14 tablets
Sancuso® (granisetron)		
3.1 mg/24 hours patch	50250035005920	2 patches
Varubi™ (rolapitant)		
90 mg tablet	50280050200320	4 tablets
Zofran® (ondansetron)		
4 mg tablet[a]	50250065050310	21 tablets
8 mg tablet[a]	50250065050320	21 tablets
24 mg tablet[ab]	50250065050340	1 tablet
4 mg/5 mL oral solution[a]	50250065052070	100 mL (2 bottles)
Zofran® ODT (ondansetron)		
4 mg orally disintegrating tablet[a]	50250065007220	21 tablets
8 mg orally disintegrating tablet[a]	50250065007240	21 tablets
Zuplenz® (ondansetron)		
4 mg oral soluble film	50250065008220	20 films (2 boxes of 10)

Brand (generic)	GPI	Quantity Per 30 Day Limit
8 mg oral soluble film	50250065008240	20 films (2 boxes of 10)

a - generic available and included in quantity limit program
b - 24 mg tablet available as generic only

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Quantities above the program set limit for **Anzemet, granisetron, Zofran/Zofran ODT/ondansetron, or Zuplenz** will be approved when ONE of the following is met:

1. The patient has cancer chemotherapy related nausea and vomiting and will be receiving chemotherapy more than 7 days per month **OR**
2. The patient has delayed emesis in highly emetogenic chemotherapy **OR**
3. The patient has hyperemesis gravidarum **OR**
4. The patient has radiation therapy induced nausea and vomiting for radiation treatment that extends beyond 7 days per month **OR**
5. The prescriber has submitted documentation in support of the requested therapeutic use and quantity for the requested agent, which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

Quantities above the program set limit for **Sancuso** will be approved when ONE of the following is met:

1. The patient has cancer chemotherapy related nausea and vomiting and will be receiving chemotherapy more than 14 days per month **OR**
2. The prescriber has submitted documentation in support of the requested therapeutic use and quantity for the requested agent, which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

Quantities above the program set limit for **Akynzeo**, **Emend, or Varubi** will be approved when ONE of the following is met:

1. The patient has cancer chemotherapy related nausea and vomiting and the patient will be receiving chemotherapy more than 7 days per month **OR**
2. The prescriber has submitted documentation in support of the requested therapeutic use and quantity for the requested agent, which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

Quantities above the program set limit for **Cesamet** will be approved when ONE of the following is met:

1. BOTH of the following:
    a. The patient has a documented history of failure to respond adequately to one conventional antiemetic treatment (Akynzeo, Anzemet, Emend, granisetron, Sancuso, Varubi, or Zofran/Zofran ODT/ondansetron) **AND**
    b. The prescriber has submitted documentation in support of use for cancer chemotherapy related nausea and vomiting and the patient will be receiving chemotherapy more than 7 days per month

    OR

2. The prescriber has submitted documentation in support of the requested therapeutic use and quantity for the requested agent, which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE[1-8,19,20]

Agent	FDA Indication(s)	Dosing and Administration
Akynzeo® (netupitant/palonosetron) capsules	• Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy	1 capsule administered approximately 1 hour prior to the start of chemotherapy
Anzemet® (dolasetron) tablets	• Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses in adults and children 2 years of age and older	Adults: 100 mg orally one hour before chemotherapy Pediatrics 2-16 years old: 1.8 mg/kg given within one hour before chemotherapy, up to a maximum of 100 mg
Cesamet® (nabilone) capsules	• Treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments	1 or 2 mg twice daily; initial dose to be given 1 to 3 hrs before chemo; may give a dose the night before; maximum daily dose is 6 mg divided in 3 doses
Emend® * (aprepitant) capsules, oral suspension	Emend capsules • In combination with other antiemetic agents, in patients 12 years of age and older for the prevention of: ○ Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy including high-dose cisplatin(HEC) including high-dose cisplatin • Prevention of postoperative nausea and vomiting (PONV) in adults Emend oral suspension • In combination with other antiemetic agents, in patients 6 months of age and older for the prevention of: ○ Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin ○ Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)	Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) • Adults and pediatric patients 12 years of age and older: 125 mg on Day 1 and 80 mg on Days 2 and 3 • Oral suspension in pediatric patients 6 months to less than 12 years of age or pediatric and adult patients unable to swallow capsules PONV • Adults: 40 mg capsules within 3 hours prior to induction of anesthesia
granisetron*	• Prevention of nausea and/or vomiting associated with initial	2 mg orally once daily or 1 mg orally twice daily

Agent	FDA Indication(s)	Dosing and Administration
tablets	and repeat courses of emetogenic cancer therapy, including high dose cisplatin • Prevention of nausea and/or vomiting associated with radiotherapy	
Sancuso® (granisetron) transdermal patch	• Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days	Apply a single patch a minimum of 24 hours before chemotherapy. Patch can be worn for up to 7 days and should be removed 24 hours after the end of chemotherapy
Varubi™ (rolapitant) tablets	• Used in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy	180 mg administered approximately 1 to 2 hours prior to the start of chemotherapy
Zofran®/ Zofran ODT®/ ondansetron* tablets, orally disintegrating tablets, oral solution	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m^2 • Prevention of nausea and/or vomiting associated with initial and repeat courses of moderately emetogenic cancer therapy • 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	Highly emetogenic chemo: 24 mg 30 minutes before chemo Moderately emetogenic chemo: 8 mg twice daily Radiotherapy: 8 mg three times daily Postoperative: 16 mg one hour before anesthesia
Zuplenz® (ondansetron) oral soluble film	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy • Prevention of nausea and vomiting associated with initial and repeat courses of moderate emetogenic cancer chemotherapy, including high dose cisplatin • Prevention of nausea and vomiting associated with	Highly emetogenic chemo: 24 mg 30 minutes before chemo Moderately emetogenic chemo: 8 mg twice daily Radiotherapy: 8 mg three times daily Postoperative: 16 mg one hour before

Agent	FDA Indication(s)	Dosing and Administration
	radiotherapy in patients receiving total body irradiation, single high-dose fraction to abdomen, or daily fractions to abdomen • Prevention of postoperative nausea and/or vomiting	anesthesia

* generics available

Cesamet capsules are to be used in patients who have failed to respond adequately to conventional antiemetic treatments. This restriction is required because a substantial proportion of any group of patients treated with Cesamet can be expected to experience disturbing psychotomimetic reactions not observed with other antiemetic agents. Because of its potential to alter the mental state, Cesamet is intended for use under circumstances that permit close supervision of the patient by a responsible individual particularly during initial use of Cesamet and during dose adjustments; it is are not intended to be used on an as needed basis or as a first antiemetic product prescribed for a patient.[6]

Cesamet contains nabilone, which is controlled in Schedule II of the Controlled Substances Act. Schedule II substances have a high potential for abuse. Prescriptions for Cesamet should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days). As with all controlled drugs, prescribers should monitor patients receiving nabilone for signs of excessive use, abuse and misuse. Patients who may be at increased risk for substance abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse) or mental illness.[6]

CLINICAL RATIONALE

Guidelines

Multiple randomized clinical trials along with current guidelines in antiemesis demonstrate that granisetron (oral and injectable), ondansetron (oral and injectable), and dolasetron (oral) are largely therapeutically equivalent and considered first line treatment for chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV) and postoperative nausea and vomiting (PONV) and are associated with relatively few mild adverse events.[9-11]

Chemotherapy Induced Nausea and Vomiting (CINV)

Guidelines from the National Comprehensive Cancer Network (NCCN) suggest when a serotonin antagonist is used as part of an antiemetic regimen that does not include an NK-1 antagonist, palonosetron is the preferred serotonin (5-HT3) antagonist. Compared to the other 5-HT3 antagonists (i.e., ondansetron, granisetron, dolasetron), palonosetron has a longer half life, prolonged inhibition of the 5-HT3 receptor, and greater binding affinity for the receptor.[10]

The NCCN recommends the following for CINV:[10]

Emetic Risk	Antiemetic Therapy
IV Chemotherapy Acute and Delayed Emesis Prevention	
High Emetic Risk	aprepitant + 5-HT3 + DEX
	fosaprepitant + 5-HT3 + DEX
	rolapitant + 5-HT3 + DEX
	netupitant/palonosetron + DEX
	olanzapine + palonosetron IV +DEX
	aprepitant or fosaprepitant IV + 5-HT3 + DEX + olanzapine
Moderate Emetic Risk	5-HT3 + DEX
	aprepitant + 5-HT3 + DEX
	fosapreitant IV + 5-HT3 + DEX

Emetic Risk	Antiemetic Therapy
	rolapitant + 5-HT3 + DEX
	netupitant/palonsetron + DEX
	olanzapine + palonosetron IV +DEX
Low Emetic Risk	DEX
	metoclopramide
	prochlorperazine
	5-HT3
Minimal Emetic Risk	No routine prophylaxis
Oral Chemotherapy Acute and Delayed Emesis Prevention	
High to Moderate Emetic Risk	5-HT3
Low to Minimal Emetic Risk (PRN recommended)	5-HT3
	metoclopramide
	prochlorperazine
Breakthrough Treatment	
Breakthrough Treatment Add one agent from a different drug class to the current regimen	5-HT3 (dolasetron, granisetron, ondansetron)
	Atypical antipsychotics (olanzapine)
	Benzodiazepeine (lorazepam)
	Cannabinoid (dronabinol, nabilone)
	Steroid (DEX)
	Phenothiazine (prochlorperazine, promethazine)
	Other (haloperidol, metoclopramide, scopolamine patch)

NK1 = neurokinin 1 antagonist; 5-HT3 = Serotonin 5-HT3 antagonist; DEX = dexamethasone

In a comparative clinical trial, the granisetron transdermal patch was shown to be non-inferior to oral granisetron in the prevention of nausea and vomiting.[4] The granisetron transdermal patch must be applied 24-48 hours before the start of chemotherapy. Patients often have blood counts tested on the day of chemotherapy and if they do not qualify for chemotherapy that day, the patch may be wasted. The manufacturer of the granisetron patch does provide free replacement patches to patients that waste one.[4]

Postoperative Nausea and Vomiting (PONV)

The Society of Ambulatory Anesthesiology 2014 guideline for the management of PONV states the following: [11]

Recommended pharmacologic antiemetics for PONV prophylaxis in adults include 5-HT3 receptor antagonists (ondansetron, dolasetron, granisetron, palonosetron), NK-1 receptor antagonists (e.g., aprepitant), corticosteroids (dexamethasone, methylprednisolone), butyrophenones (droperidol, haloperidol), antihistamines (dimenhydrinate, meclizine), and anticholinergics (transdermal scopolamine [TDS]).[11]

An algorithm on prevention and treatment strategies considers patient preferences, baseline risks, and cost effectiveness, but does not prefer one agent over others in all patients. While PONV prevention is recommended in a subset of patients, current evidence does not support giving prophylactic antiemetics to all patients who undergo surgical procedures. If prophylaxis fails or was not received, use of an antiemetic from a different class than prophylactic drug is recommended. Combination therapy for PONV prophylaxis is preferable to using a single drug alone.[11]

Although ondansetron has been considered the "gold standard" compared with other antiemetics, it is less effective than aprepitant for reducing emesis and palonosetron for the incidence of PONV. Palonosetron 0.075 mg is more effective than granisetron 1 mg and ondansetron 4 mg in preventing PONV. Ondansetron, dolasetron, granisetron, and tropisetron

are most effective in the prophylaxis of PONV when given at the end of surgery, although some data on dolasetron suggest timing may have little effect on efficacy. Palonosetron is typically given at the start of surgery.[11]

In 2 large RCTs, aprepitant was similar to ondansetron in achieving complete response (no vomiting and no use of rescue antiemetic) for 24 hours after surgery. However, aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and in reducing nausea severity in the first 48 hours after surgery. It also has a greater antiemetic effect compared with ondansetron.[11]

Radiation Induced Nausea and Vomiting (RINV)
The American Society of Clinical Oncology (ASCO) Practice Guidelines for Antiemetics in Oncology recommends that for patients who receive high-risk radiation therapy, patients receive a 5-HT3 antagonist before each radiation fraction and at least 24 hours after completing radiation therapy. Patients should also be given a five-day course of dexamethasone during fractions one to five.[9]

The NCCN recommends starting pretreatment for each day of radiation therapy treatment with either granisetron or ondansetron, with or without dexamethasone.

Nausea and Vomiting of Pregnancy
American College of Obstetricians and Gynecologists (ACOG, 2015) recommends the following for nausea and vomiting during pregnancy:[13]

- Taking prenatal vitamins for 3 months before conception may reduce the incidence and severity of nausea and vomiting of pregnancy.
- Treatment of nausea and vomiting of pregnancy with vitamin B6 or vitamin B6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. Medications for which there are some safety data but no conclusive evidence of efficacy include anticholinergics and metoclopramide. Evidence is limited on the safety or efficacy of the 5-HT3 inhibitors (e.g., ondansetron) for nausea and vomiting of pregnancy; however, because of their effectiveness in reducing chemotherapy-induced emesis, their use appears to be increasing.

REFERENCES

1. Anzemet prescribing information. Sanofi Aventis. September 2014.
2. Granisetron (tablets) prescribing information. Teva Pharmaceuticals. August 2014.
3. Zofran prescribing information. GlaxoSmithKline. October 2016.
4. Sancuso prescribing information. ProStrakan. September 2015.
5. Emend prescribing information. Merck & Co., Inc. January 2017.
6. Cesamet prescribing information. Meda Pharmaceuticals. September 2013.
7. Clinical Pharmacology Online: Granisol (updated 10/2015). Accessed 5/21/2016.
8. Zuplenz prescribing information. Praelia Pharmaceuticals, Inc. September 2014.
9. Basch E, Prestrud AA, Hesketh PJ, et al. American Society of Clinical Oncology clinical practice guidelines update 2011. Accessed 4/17/2012 @ www.asco.org/guidelines/antiemetics.
10. National Comprehensive Cancer Network (NCCN). Antiemesis Guidelines in Oncology. Version 2.2017. Accessed 5/23/2017.
11. The Society of Ambulatory Anesthesiology 2014 guideline for the Management of PONV. *Anesth Analg;.* 2014 118(1):85-113.
12. American College of Obstetrician and Gynecologists (ACOG). ACOG Practice Bulletin: Nausea and Vomiting of Pregnancy. *Obstet Gynecol. 2015;106(3):e12-e24*.
13. FDA. Drug safety communication: Abnormal heart rhythms associated with the use of Anzemet (dolasetron mesylate). Issued 12/17/2010. Accessed 5/30/2017 @ http://www.fda.gov/Drugs/DrugSafety/ucm237081.htm

14. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med* 2013;368:814-823.
15. A Register Based Nationwide Control Study. International Society of Pharmaco-epidemiology. Montreal, Canada; 2013. Abstract 25, Pregnancy session 1.
16. Anderka M, Mitchell AA, Louik C, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol*. 2012;94(1):22-30.
17. FDA Safety Information-Serotonin-3 (5-HT3) Receptor Antagonists. September 2014. Accessed 3/31/2015 at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm418818.htm
18. Akynzeo prescribing information. Helsinn Therapeutics, Inc. December 2016.
19. Varubi prescribing information. Tesaro, Inc. September 2015.