BlueCross BlueShield of Alabama

Antiemetic Agents Quantity Limit Program Summary

This program applies to Commercial, GenPlus, NetResults A series, Blue Partner, 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, 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	Multisource Code
Akynzeo® (netupitant/palonosetron)			
300 mg / 0.5 mg	50309902290120	2 capsules	M, N, O, or Y
Anzemet® (dolasetron)			
50 mg tablet	50250025200320	7 tablets	M, N, O, or Y
100 mg tablet	50250025200330	7 tablets	M, N, O, or Y
Cesamet® (nabilone)			
1 mg capsule	50300040000110	42 capsules	M, N, O, or Y
Emend® (aprepitant)			
80 mg capsule[a]	50280020000120	4 capsules	M, N, O, or Y
125 mg capsule[a]	50280020000130	2 capsules	M, N, O, or Y
Emend Therapy Pack (1x125 mg capsule, 2x80 mg capsules)[a]	50280020006320	6 capsules (2 therapy packs)	M, N, O, or Y
125mg/5mL oral suspension	50280020001930	6 single-use kits	M, N, O, or Y
granisetron			
1 mg tablet[a]	50250035100310	14 tablets	M, N, O, or Y
Sancuso® (granisetron)			
3.1 mg/24 hours patch	50250035005920	2 patches	M, N, O, or Y
Varubi® (rolapitant)			
90 mg tablet	50280050200320	4 tablets	M, N, O, or Y
Zofran® (ondansetron)			
4 mg tablet[a]	50250065050310	21 tablets	M, N, O, or Y
8 mg tablet[a]	50250065050320	21 tablets	M, N, O, or Y
24 mg tablet[ab]	50250065050340	1 tablet	M, N, O, or Y
4 mg/5 mL oral solution[a]	50250065052070	100 mL (2 bottles)	M, N, O, or Y
Zofran® ODT (ondansetron)			
4 mg orally disintegrating tablet[a]	50250065007220	21 tablets	M, N, O, or Y
8 mg orally disintegrating tablet[a]	50250065007240	21 tablets	M, N, O, or Y
Zuplenz® (ondansetron)			
4 mg oral soluble film	50250065008220	20 films (2 boxes of 10)	M, N, O, or Y

Brand (generic)	GPI	Quantity Per 30 Day Limit	Multisource Code
8 mg oral soluble film	50250065008240	20 films (2 boxes of 10)	M, N, O, or Y

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. ALL 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 requested agent will be used in addition to the patient's current regimen for cancer chemotherapy related nausea and vomiting
AND
C. 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

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The purpose of 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[1-7,12,13]

Agent	FDA Indication(s)	Dosing and Administration
Akynzeo® (netupitant/palonosetron) capsules	• In combination with dexamethasone for the 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 (HEC) including high-dose cisplatin ○ Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) • 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	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: 3 mg/kg on Day 1 (maximum dose 125 mg) and 2 mg/kg on Days 2 and 3 (maximum dose 80 mg) **Prevention Postoperative Nausea and Vomiting (PONV)** • Adults: 40 mg capsules within 3 hours prior to induction of anesthesia

Agent	FDA Indication(s)	Dosing and Administration
	associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) Limitations of use: • Emend has not been studied for treatment of established nausea and vomiting Chronic continuous administration of Emend is not recommended	
granisetron* tablets	• Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high dose cisplatin • Prevention of nausea and/or vomiting associated with radiotherapy	2 mg orally once daily or 1 mg orally twice daily
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 within 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	Highly emetogenic chemo: 24 mg 30 minutes before chemotherapy Moderately emetogenic chemotherapy: 8 mg twice daily Radiotherapy: 8 mg three times daily Postoperative: 16 mg one hour before anesthesia

Agent	FDA Indication(s)	Dosing and Administration
	• Prevention of postoperative nausea and/or vomiting	
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 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	Highly emetogenic chemo: 24 mg 30 minutes before chemotherapy Moderately emetogenic chemotherapy: 8 mg twice daily Radiotherapy: 8 mg three times daily Postoperative: 16 mg one hour before anesthesia

* generics available

CLINICAL RATIONALE
Guidelines
Multiple randomized clinical trials along with current guidelines in antiemesis demonstrate that granisetron (oral and injectable), ondansetron (oral and injectable), palonosetron (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.[8-10]

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. Cesamet contains nabilone which is a synthetic cannabinoid. 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]

The American Society of Clinical Oncology states cannabis-based medication may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, methodological limitations of the trials limit their conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions. At this time, these guidelines recommend 5-HT3 receptor agonists, dexamethasone, NK-1receptor agonists, and olanzapine for the prevention of nausea and vomiting after chemotherapy. Cannabinoids should be reserved for patients who are intolerant or refractory to first-line therapy.

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]

Chemotherapy Induced Nausea and Vomiting (CINV)
Chemotherapy induced nausea and vomiting (CINV) can have significant impact on a patient's compliance and/or ability to complete potentially useful or curative anticancer treatment. The incidence and severity is affected by several factors including specific chemotherapy agents, dose, route of administration, schedule of administration, radiation target, and patient variability (age, sex, prior chemotherapy, history of alcohol use, etc.). In highly emetogenic regimens more than 90% of patients will experience episodes of vomiting but only about 30% will do so when given antiemetic prophylactic therapy.[9]

Vomiting is triggered by afferent impulses to the vomiting center from the chemoreceptor trigger zone, pharynx and gastrointestinal tract (GI), and cerebral cortex. The principle chemoreceptors involved in the emetic response are the serotonin and dopamine receptors. Additional neuroreceptors stimulated include acetylcholine, corticosteroid, histamine, cannabinoid, opioid, and neurokinin-1 receptors. Due to the variety of receptors involved and no final common pathway for emesis identified, multiple agents are used to block different pathways to provide a synergistic effect in an antiemesis prophylactic regimen.[9]

There are several identified classes of chemotherapy-induced nausea and vomiting including acute onset (typically occurs within the first few minutes to hours after chemotherapy administration), delayed onset (occurs more than 24 hours after chemotherapy dosing), anticipatory (occurs prior to chemotherapy administration and is considered a conditioned response), breakthrough (occurs despite prophylactic treatment and requires "rescue" antiemetic agents), and refractory (occurs during subsequent chemotherapy treatment cycles despite prophylactic and rescue therapy).[9]

NCCN Guidelines recommend antiemetic therapy begins prior to chemotherapy and continues for the same length of time as the duration of the emetic activity of the drug given. The frequency of chemotherapy induced emesis depends mostly on the potential for the regimen to cause nausea and vomiting. Many chemotherapy regimens have been categorized by their potential to cause emesis. The classification (i.e., high, moderate, low, minimal) is based on the percentage of patients that experience acute emesis. Highly emetogenic risk is defined as 90% or more of patients, moderate risk has 30%-90% of patients, low risk is between 10% and 30% of patients, and minimal risk is <10% of patients experience acute emesis.[9]

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, either palonosetron or granisetron extended-release injection is the preferred serotonin (5-HT3) antagonist. Compared to the other 5-HT3 antagonists [i.e., ondansetron, granisetron (tablets, intravenous injection), dolasetron, due to longer half-life, and prolonged inhibition of the 5-HT3 receptor].[9]

The NCCN recommends the following for CINV:[9]

Emetic Risk	**Antiemetic Therapy**
IV Chemotherapy Acute and Delayed Emesis Prevention	
High Emetic Risk	NK-1RA + 5-HT3 + DEX
	netupitant/palonosetron + DEX
	olanzapine + palonosetron IV +DEX
	NK-1RA + 5-HT3 + DEX + olanzapine
	netupitant/palonosetron + DEX + olanzapine
Moderate Emetic Risk	5-HT3 + DEX

Emetic Risk	Antiemetic Therapy
	NK-1RA + 5-HT3 + DEX
	netupitant/palonsetron + DEX
	olanzapine + palonosetron IV +DEX
Low Emetic Risk	DEX
	metoclopramide
	prochlorperazine
	5-HT3 (excluding palonosetron IV)
Minimal Emetic Risk	No routine prophylaxis
Oral Chemotherapy Acute and Delayed Emesis Prevention	
High to Moderate Emetic Risk	5-HT3 (excluding palonosetron IV)
Low to Minimal Emetic Risk (PRN recommended)	5-HT3 (excluding palonosetron IV)
	metoclopramide
	prochlorperazine
Breakthrough Treatment	
Breakthrough Treatment Add one agent from a different drug class to the current regimen	dolasetron, granisetron, ondansetron (5-HT3)
	olanzapine (atypical antipsychotic)
	lorazepam (benzodiazepine)
	dronabinol, nabilone (cannabinoid)
	DEX (steroid)
	prochlorperazine, promethazine (phenothiazine)
	haloperidol, metoclopramide, scopolamine patch (other)

NK-1RA (aprepitant, fosaprepitant, rolapitant) = neurokinin 1 antagonist; 5-HT3 = Serotonin 5-HT3 antagonist (dolasetron, granisetron, ondansetron, palonosetron IV); 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)[10]

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

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]).

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.

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.

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.[8]

The NCCN recommends starting pretreatment for each day of radiation therapy treatment with either granisetron or ondansetron, with or without dexamethasone.[9]

Nausea and Vomiting of Pregnancy[11]
American College of Obstetricians and Gynecologists (ACOG, 2015) recommends the following for nausea and vomiting during pregnancy:

- 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.

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12. Akynzeo prescribing information. Helsinn Therapeutics, Inc. April 2018.
13. Varubi prescribing information. Tesaro, Inc. April 2018.

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