Antiemetic Agents Quantity Limit Program Summary

This program applies to Medicaid.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
11/1/2023	5/1/2017

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Akynzeo® (netupitant/palonosetron) Capsule	• In combination with dexamethasone in adults 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
Anzemet® (dolasetron) Tablet	• 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		2
Emend® (aprepitant) Capsule* 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) 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) Limitations of use: • Emend has not been studied for treatment of established nausea and vomiting • Chronic continuous administration of Emend is not recommended	*generics available	3

Agent(s)	FDA Indication(s)	Notes	Ref#
granisetron** Tablet	• 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	**available as generic only	4
ondansetron** Tablet Oral disintegrating tablet 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	** available as generic only	7, 15
Sancuso® (ganisetron) Transdermal patch	• Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days		5
Varubi® (rolapitant) Tablet	• 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		6
Zuplenz® (ondansetron) Oral soluble film	• 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 vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in adults and pediatric patients 4 years of age and older • Prevention of nausea and vomiting associated with radiotherapy in adult patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to abdomen • Prevention of postoperative nausea and/or vomiting		8

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

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.(9-11)
Chemotherapy and Radiation Therapy Induced Nausea and Vomiting	Nausea and vomiting caused by anticancer agents and/or radiation therapy (RT) can have significant impact on a patient's quality of life, leading to poor compliance with further anticancer agents and/or RT. In addition, nausea and/or vomiting can result in dehydration, metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient's performance status and mental

	status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.(9) The incidence and severity of nausea and/or vomiting in patients receiving anticancer agents and/or RT are 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.(10) Vomiting is triggered by afferent impulses to the vomiting center from the chemoreceptor trigger zone, pharynx and gastrointestinal tract (GI), and cerebral cortex. The principal 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.(10) There are several identified classes of CINV 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).(10) National Comprehensive Cancer Network (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. High 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 less than 10% of patients experience acute emesis.(10) 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) NCCN recommends starting pretreatment for each day of radiation therapy treatment with either granisetron or ondansetron, with or without dexamethasone.(10)

NCCN suggests when a serotonin (5-HT3) 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 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.(10)

NCCN and ASCO recommend the following for CINV and RINV:(9-10)

Emetic Risk	Antiemetic Therapy
IV Chemotherapy Acute and Delayed Emesis Prevention	
High Emetic Risk	olanzapine + NK-1RA + 5-HT3 + DEX (preferred)
	olanzapine + palonosetron IV +DEX
	NK-1RA + 5-HT3 + DEX
Moderate Emetic Risk	5-HT3 + DEX
	NK-1RA + 5-HT3 + 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	Oral 5-HT3
Low to Minimal Emetic Risk	Oral 5-HT3
	metoclopramide
(PRN recommended)	prochlorperazine
Breakthrough Treatment	
Breakthrough Treatment	olanzapine (atypical antipsychotic) (preferred)
Add one agent from a different drug class to the current regimen	dolasetron, granisetron, ondansetron (5-HT3)
	lorazepam (benzodiazepine)
	dronabinol, nabilone (cannabinoid)
	DEX (steroid)
	prochlorperazine, promethazine (phenothiazine)
	haloperidol, metoclopramide, scopolamine patch (other)
Radiation-induced	
Radiation therapy – upper abdomen/localized sites	Oral granisetron ± DEX
	Oral ondansetron ± DEX
Total body irradiation	Oral granisetron ± DEX
	Oral ondansetron ± DEX
Chemotherapy and radiation therapy	See emesis prevention for chemotherapy-induced nausea/vomiting
Pediatric patients	
High emetic risk	5-HT3 + DEX + aprepitant
	5-HT3 + DEX + fosaprepitant

		5-HT3 + DEX
		palonosetron + aprepitant
		palonosetron + fosaprepitant
	Moderate emetic risk	5-HT3 +DEX
		5-HT3 +aprepitant
		5HT-3 + fosaprepitant
	Low emetic risk	ondansetron
		granisetron
	Minimal emetic risk	Should not be offered routine antiemetic prophylaxis

NK-1RA (aprepitant, fosaprepitant, netupitant, 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.(5)

Postoperative Nausea and Vomiting

Nausea and vomiting are two of the most common adverse events in the postoperative period with an estimated incidence of 30% in the general surgical population and as high as 80% in high risk patients. Unresolved postoperative nausea and vomiting (PONV) is a highly distressing experience and may result in prolonged post anesthesia care unit stay and unanticipated hospital admission that leads to a significant increase in overall health care costs. The goal of PONV prophylaxis is to decrease the incidence of PONV, patient-related distress, and health-care costs.(11)

Optimal management of PONV is a complex process. There are numerous antiemetics with varying pharmacokinetics, efficacy, and side-effect profiles, thus the choice of an antiemetic will depend on the clinical context. The benefit of PONV prophylaxis also needs to be balanced with the risk of adverse effects. At an institutional level, the management of PONV is also influenced by factors such as cost-effectiveness, drug availability, and drug formulary decisions.(11)

The Society for Ambulatory Anesthesiology has published Consensus Guidelines for the management of postoperative nausea and vomiting. The goals of these guidelines include:(12)

- Identification of reliable predictors of PONV risks in adults and postoperative vomiting in children
- Establishment of interventions which reduce baseline risks for PONV
- Identify the most effective antiemetic single therapy and combination therapy regimens for PONV prophylaxis
- Evaluation of the efficacy of PONV and post-discharge nausea and vomiting (PDNV) treatment with or without prior PONV prophylaxis
- Determination of the optimal dosing and timing of antiemetic prophylaxis
- Appraisal of the cost-effectiveness of PONV management strategies
- Creating an algorithm to summarize the risk stratification, risk reduction, prophylaxis, and treatment of PONV
- Evaluating the management of PONV recovery pathways

	• Proposal of a research agenda for future studies Risk for PONV in adults can be identified using an assessment called Apfel's simplified risk score for identification of high-risk patients.(11,13) Patients are given 1 point for each of the following when met: • Female gender • Non-smoker • History of PONV and/or motion sickness • Postoperative opioids A score of 0, 1, 2, 3, and 4 correlates with an approximate risk of PONV of 10%, 20%, 40%, 60% and 80% respectively. Patients with a score of 0-1 are classified as low risk, a score of 2 is medium risk, and a score of 3-4 indicates high risk.(11,13) Risk for PDNV in adults can also be assessed using an assessment also by Apfel et al. Patients are given 1 point for each of the following when met:(11,13) • Female gender • History of PONV • Age less than 50 • Use of opioids in postanesthesia care unit (PACU) • Nausea in PACU A score of 0, 1, 2, 3, 4, or 5 correlates with an approximate risk of PDNV of 10%, 20%, 30%, 50%, 60%, and 80% respectively.(11,13) The risk factors for POV/PONV in children are different from those in adults. Pediatric patients are evaluated using a Simplified Risk Score from Eberhart et al.(11,14) Similar to the adult risk factor assessments, patients are given 1 point for each risk factor met. • Surgery greater than or equal to 30 minutes • Age greater than or equal to 3 years • Strabismus surgery • History of POV or family history of PONV A score of 0, 1, 2, 3, or 4 correlates with an approximate risk of POV of 10%, 10%, 30%, 50%, and 70% respectively.(11,14) The guidelines recommend the use of multimodal prophylaxis in patients with one or more risk factors for PONV. Patients with 1-2 risk factors for PONV should receive 2 agents for prophylaxis of PONV and patients with greater than 2 risk factors should receive 3-4 agents for prophylaxis. Ondansetron is the most commonly used and

	studied 5-HT_3 receptor antagonist and is considered the gold standard in PONV management.(11) There is not sufficient evidence for the guidelines to guide the clinician to select the most effective individual antiemetic over other combination therapies with the exception of using agents from a different pharmacologic class. Recommended agents for adults and children (listed in alphabetical order) are: Note not all products are available in the United States and not all products are FDA labeled for PONV(11) Adults • Amisulpride (IV) • Aprepitant (oral) • Casopitant (oral) • Dexamethasone (IV) • Dimenhydrinate (IV) • Dolasetron (IV) • Droperidol (IV) • Ephedrine (IM) • Granisetron (IV) • Haloperidol (IM/IV) • Methylprednisolone (IV) • Metoclopramide (oral) • Ondansetron (IV or oral disintegrating tablet) • Palonosetron (IV) • Perphenazine (IV) • Promethazine (oral) • Ramosetron (IV) • Rolapitant (oral) • Scopolamine (transdermal patch) • Tropisetron (IV) Pediatrics • Aprepitant (IV) • Dexamethasone (IV) • Dimenhydrinate (IV) • Dolasetron (IV) • Droperidol (IV) • Granisetron (IV) • Ondansetron (IV) • Palonosetron (IV) • Tropisetron (IV)
Nausea and Vomiting of Pregnancy(12)	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

Safety(1-8, 15)	• **Akynzeo** (netupitant and palonosetron) has no FDA labeled contraindications
	• **Anzemet** (dolasetron mesylate) is contraindicated in:
	  ○ Patients known to have hypersensitivity to the drug
	• **Emend** (aprepitant) is contraindicated in:
	  ○ Known hypersensitivity to any component of this drug
	  ○ Concurrent use with pimozide
	• **Granisetron** is contraindicated in:
	  ○ Patients with known hypersensitivity to the drug or any of its components
	• **Sancuso** (granisetron) is contraindicated in:
	  ○ Known hypersensitivity to granisetron or to any of the components of the transdermal system
	• **Varubi** (rolapitant) is contraindicated in:
	  ○ Use with CYP2D6 substrates with narrow therapeutic index (e.g., thioridazine and pimozide)
	• **Zuplenz/ondansetron** is contraindicated in:
	  ○ Patients known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any components of the formulation
	  ○ Concomitant use of apomorphine

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Number	Reference
1	Akynzeo prescribing information. Helsinn Therapeutics, Inc. June 2021.
2	Anzemet prescribing information. Sanofi Aventis. June 2021.
3	Emend prescribing information. Merck & Co., Inc. May 2022.
4	Granisetron (tablets) prescribing information. Natco Pharma Limited. October 2019.
5	Sancuso prescribing information. Kyowa Kirin, Inc. December 2022.
6	Varubi prescribing information. Tesaro, Inc. August 2020.
7	Ondansetron solution prescribing information. Hikma Pharmaceuticals USA Inc. October 2021.
8	Zuplenz prescribing information. Praelia Pharmaceuticals, Inc. August 2021.
9	Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. J Clin Oncol 2020 38:24/,2782-2797
10	National Comprehensive Cancer Network (NCCN). Antiemesis Guidelines. Version 2.2022.
11	Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. International Anesthesia Research Society. August 2020. Volume 131. Number 2.
12	American College of Obstetrician and Gynecologists (ACOG). ACOG Practice Bulletin: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;106(3):e12-e24.
13	Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693–700.
14	Eberhart LH, Geldner G, Kranke P, et al. The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients. Anesth Analg. 2004;99:1630–1637.
15	Ondansetron tablets/orally disintegrating tablets prescribing information. Glenmark Pharmaceuticals Inc, USA. November 2021.

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
	Aprepitant Capsule 125 MG	125 MG	2	Capsules	30	DAYS			
	Dolasetron Mesylate Tab 100 MG		7	Tablets	30	DAYS			
	Granisetron HCl Tab 1 MG	1 MG	14	Tablets	30	DAYS			
	Ondansetron HCl Oral Soln 4 MG/5ML	4 MG/5ML	100	mLs	30	DAYS			
	Ondansetron HCl Tab 24 MG	24 MG	1	Tablet	30	DAYS			
	Ondansetron HCl Tab 8 MG	8 MG	21	Tablets	30	DAYS			
	Ondansetron Orally Disintegrating Tab 4 MG	4 MG	21	Tablets	30	DAYS			
	Ondansetron Orally Disintegrating Tab 8 MG	8 MG	21	Tablets	30	DAYS			
Akynzeo	Netupitant-Palonosetron Cap 300-0.5 MG	300-0.5 MG	2	Capsules	30	DAYS			
Anzemet	Dolasetron Mesylate Tab 50 MG	50 MG	7	Tablets	30	DAYS			
Emend	Aprepitant Capsule 80 MG	80 MG	4	Capsules	30	DAYS			
Emend	Aprepitant For Oral Susp 125 MG (125 MG/5ML)	125 MG/5ML	6	Kits	30	DAYS			
Emend tripack	Aprepitant Capsule Therapy Pack 80 & 125 MG	80 & 125 MG	2	Packs	30	DAYS			
Sancuso	Granisetron TD Patch 3.1 MG/24HR (Contains 34.3 MG)	3.1 MG/24HR	2	Patches	30	DAYS			
Varubi	Rolapitant HCl Tab Therapy Pack 2 x 90 MG (Base Equiv)	90 MG	4	Tablets	30	DAYS			
Zofran	Ondansetron HCl Tab 4 MG	4 MG	21	Tablets	30	DAYS			
Zuplenz	Ondansetron Oral Soluble Film 4 MG	4 MG	20	Films	30	DAYS			
Zuplenz	Ondansetron Oral Soluble Film 8 MG	8 MG	20	Films	30	DAYS			

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	Aprepitant Capsule 125 MG	125 MG	Medicaid
	Dolasetron Mesylate Tab 100 MG		Medicaid
	Granisetron HCl Tab 1 MG	1 MG	Medicaid
	Ondansetron HCl Oral Soln 4 MG/5ML	4 MG/5ML	Medicaid
	Ondansetron HCl Tab 24 MG	24 MG	Medicaid
	Ondansetron HCl Tab 8 MG	8 MG	Medicaid

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	Ondansetron Orally Disintegrating Tab 4 MG	4 MG	Medicaid
	Ondansetron Orally Disintegrating Tab 8 MG	8 MG	Medicaid
Akynzeo	Netupitant-Palonosetron Cap 300-0.5 MG	300-0.5 MG	Medicaid
Anzemet	Dolasetron Mesylate Tab 50 MG	50 MG	Medicaid
Emend	Aprepitant Capsule 80 MG	80 MG	Medicaid
Emend	Aprepitant For Oral Susp 125 MG (125 MG/5ML)	125 MG/5ML	Medicaid
Emend tripack	Aprepitant Capsule Therapy Pack 80 & 125 MG	80 & 125 MG	Medicaid
Sancuso	Granisetron TD Patch 3.1 MG/24HR (Contains 34.3 MG)	3.1 MG/24HR	Medicaid
Varubi	Rolapitant HCl Tab Therapy Pack 2 x 90 MG (Base Equiv)	90 MG	Medicaid
Zofran	Ondansetron HCl Tab 4 MG	4 MG	Medicaid
Zuplenz	Ondansetron Oral Soluble Film 4 MG	4 MG	Medicaid
Zuplenz	Ondansetron Oral Soluble Film 8 MG	8 MG	Medicaid

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Akynzeo, Emend, Varubi Standalone QL	**Quantity limit for Akynzeo, Emend, or Varubi** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has cancer chemotherapy related nausea and vomiting and the patient will be receiving chemotherapy more than 7 days per month **OR** 3. The prescriber has provided information supporting the use of the requested agent for the requested diagnosis and quantity **Length of Approval:** 12 months
Anzemet, granisetron, ondansetron/ondansetron ODT. Zuplenz Standalone QL	**Quantity limit for Anzemet, granisetron, ondansetron/ondansetron ODT, or Zuplenz** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has cancer chemotherapy related nausea and vomiting and will be receiving chemotherapy more than 7 days per month **OR** 3. The patient has delayed emesis in highly emetogenic chemotherapy **OR** 4. The patient has hyperemesis gravidarum **OR** 5. The patient has radiation therapy induced nausea and vomiting for radiation treatment that extends beyond 7 days per month **OR** 6. The prescriber has provided information supporting the use of the requested agent for the requested diagnosis and quantity **Length of Approval**: 12 months
Sancuso Standalone QL	**Quantity limit for Sancuso** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has cancer chemotherapy related nausea and vomiting and will be receiving chemotherapy more than 14 days per month **OR** 3. The prescriber has provided information supporting the use of the requested agent for the requested diagnosis and quantity **Length of Approval:** 12 months