Drug and Biologic Coverage Policy

Effective Date 7/15/2022
Next Review Date… 7/15/2023
Coverage Policy Number 1705

Antiemetic Therapy

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Related Coverage Resources

Quantity Limitations – (1201)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, 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 customer'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 customer's benefit plan document always supersedes 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 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. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Antiemetic Therapy includes the following products:

- **Akynzeo®** (palonosetron/fosnetupitant) injection
- **Akynzeo®** (palonosetron/netupitant) capsule
- **Aloxi®** (palonosetron) injection
- **Anzemet®** (dolasetron) tablets
- **Cinvanti™** (aprepitant) injectable emulsion
- **Emend®** (aprepitant) capsule, suspension
- **Emend®** (fosaprepitant) injection
- **Sancuso®** (granisetron) transdermal
- **Sustol®** (granisetron extended-release) injection
- **Varubi®** (rolapitant) tablet
- **Zofran®** (ondansetron) solution, tablets
- **Zofran® ODT** (ondansetron) orally disintegrating tablets
- **Zuplenz®** (ondansetron) film

This policy addresses the use of Antiemetic Therapy. Coverage for Antiemetic Therapy products may require the use of preferred or generic products according to the customer's benefit plan. Refer to the customer's benefit plan document for coverage details.

Antiemetic Therapy is considered medically necessary when the following criteria are met:

Drug	Criteria for Use
Akynzeo (palonosetron/ fosnetupitant) injection	**Considered as medically necessary for an adult in combination with dexamethasone for the prevention of nausea and vomiting for intravenous antineoplastic therapy meeting the following:** • High emetic risk • Moderate emetic risk
Akynzeo (palonosetron/ netupitant) capsule	**Considered as medically necessary for an adult in combination with dexamethasone for the prevention of nausea and vomiting for intravenous antineoplastic therapy meeting either of the following:** • High emetic risk • Moderate emetic risk *When criteria are met, a maximum of 4 capsules will be allowed per 28 days.*
Aloxi (palonosetron) injection	**Considered as medically necessary for ANY of the following:** • Prevention of nausea and vomiting associated with cancer chemotherapy in a pediatric individual • Prevention of nausea and vomiting in combination with dexamethasone for intravenous antineoplastic therapy in an adult individual meeting either of the following: o High emetic risk o Moderate emetic risk • Prevention of post-operative nausea and vomiting (PONV) for up to 24 hours following surgery in an adult individual
Anzemet (dolasetron) tablet	Considered as medically necessary for the prevention of nausea and vomiting and treatment of breakthrough nausea and vomiting associated with low, moderate, and highly emetogenic cancer therapy.
Cinvanti (aprepitant) injectable emulsion	**Considered as medically necessary for an adult in combination with dexamethasone and a serotonin (5-HT_3) receptor antagonist for the prevention of nausea and vomiting for intravenous antineoplastic therapy meeting either of the following:** • High emetic risk • Moderate emetic risk
Emend (aprepitant) capsule, suspension	**Considered as medically necessary in an adult when both of the following are met:** • **ONE** of the following: o Prevention of nausea and vomiting in combination with dexamethasone and a serotonin (5-HT_3) receptor antagonist for intravenous antineoplastic therapy that has high or moderate emetic risk o Prevention of post-operative nausea and vomiting (PONV) in an adult • Documented intolerance or inability to use generic aprepitant capsules **Considered as medically necessary in a pediatric individual when both of the following are met:** • Prevention of nausea and vomiting associated with cancer chemotherapy in combination with a serotonin (5-HT_3) receptor antagonist • For individuals 12 years of age and older: Documented intolerance or inability to use generic aprepitant capsules *When criteria are met, the following maximum quantities will be allowed:* • *Capsules: Up to 4 treatment cycles (one 125mg capsule and two 80mg capsules) per 28 days OR one 40 mg capsule per 28 days* • *Suspension: 12 packets per 28 days (3 packets per week)*

Drug	Criteria for Use
Emend (fosaprepitant) injection	**Considered as medically necessary for an individual 6 months and older in combination with dexamethasone and a serotonin (5-HT_3) receptor antagonist for the prevention of nausea and vomiting for intravenous antineoplastic therapy meeting ONE of the following:** • High emetic risk • Moderate emetic risk
Sancuso (granisetron) transdermal	**Considered as medically necessary for an adult for either of the following:** • Prevention of nausea and vomiting for either of the following: o High or moderate emetic risk intravenous antineoplastic therapy in combination with dexamethasone o High or moderate emetic risk oral antineoplastic therapy • Breakthrough treatment of chemotherapy-induced nausea/vomiting *When criteria are met, a maximum of 4 patches will be allowed per 30 days.*
Sustol (granisetron extended-release) injection	**Considered as medically necessary for an adult in combination with dexamethasone for the prevention of nausea and vomiting for intravenous antineoplastic therapy meeting either of the following:** • High emetic risk AND Sustol will be used in combination with an NK1 receptor antagonist (i.e., aprepitant, fosaprepitant, rolapitant) • Moderate emetic risk
Varubi (rolapitant) tablet	**Considered as medically necessary for an adult in combination with dexamethasone and a serotonin (5-HT_3) receptor antagonist for the prevention of nausea and vomiting for intravenous antineoplastic therapy meeting either of the following:** • High emetic risk • Moderate emetic risk *When criteria are met, a maximum of 4 tablets (2 doses) will be allowed per 28 days.*

For Employer Group Plans: Where coverage requires the use of preferred or generic products, the following criteria apply:

Drug	Standard, Performance, or Legacy Prescription Drug List Plan	Value, Advantage, or Cigna Total Savings Prescription Drug List Plan
Zofran (ondansetron) 4 mg, 8 mg, 24 mg tablets,4 mg/5 ml solution	**BOTH** of the following: • Documented intolerance to one generic formulation of Zofran • Documented failure/inadequate response, contraindication per FDA label, intolerance, or not a candidate for granisetron tablets	
Zofran ODT (ondansetron) 4 mg, 8 mg orally disintegrating tablets	Documented intolerance or inability to use **ALL** of the following: • ondansetron 4 mg or 8 mg tablets, • ondansetron 4 mg or 8 mg orally disintegrating tablets • ondansetron 4 mg/5 ml solution	
Zuplenz (ondansetron) 4 mg and 8 mg film	Documented intolerance or inability to use **ALL** of the following: • ondansetron 4 mg or 8 mg tablets, • ondansetron 4 mg or 8 mg orally disintegrating tablets • ondansetron 4 mg/5 ml solution	

Initial and reauthorization is up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Antiemetic Therapy is considered experimental, investigational or unproven for ANY other use.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication

Product	FDA Approved Indication
Akynzeo (palonosetron/ fosnetupitant) capsule	Akynzeo capsules is indicated 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. Akynzeo capsules is a combination of palonosetron and netupitant: palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.
Akynzeo (palonosetron/ fosnetupitant) injection	Akynzeo for injection is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Akynzeo for injection is a combination of palonosetron and fosnetupitant, a prodrug of netupitant: palonosetron prevents nausea and vomiting during the acute phase and fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. Limitations of Use Akynzeo for injection has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.
Aloxi (palonosetron) injection	**Chemotherapy-Induced Nausea and Vomiting in Adults** Aloxi is indicated for: • Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses • Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses **Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients Aged 1 month to Less than 17 Years** Aloxi is indicated for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. **Postoperative Nausea and Vomiting in Adults** Aloxi is indicated for prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated. As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, Aloxi is recommended even where the incidence of postoperative nausea and/or vomiting is low.
Anzemet (dolasetron) tablet	Anzemet tablets are indicated for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses in adults and children 2 years and older.
Cinvanti	Cinvanti, in combination with other antiemetic agents, is indicated in adults for the prevention of:

Product	FDA Approved Indication
(aprepitant) injectable emulsion	• 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 Cinvanti has not been studied for the treatment of established nausea and vomiting.
Emend (aprepitant) capsule, suspension	**Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)** Emend for oral suspension, in combination with other antiemetic agents, is indicated 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). Emend capsules, in combination with other antiemetic agents, is indicated 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 cancer 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)** Emend capsules are indicated in adults for the prevention of postoperative nausea and vomiting. **Limitations of Use** • Emend has not been studied for the treatment of established nausea and vomiting. • Chronic continuous administration of Emend is not recommended because it has not been studied, and because the drug interaction profile may change during chronic continuous use.
Emend (fosaprepitant) injection	Emend for injection, in combination with other antiemetic agents, is indicated in adults and pediatric 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. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). Limitations of Use • Emend has not been studied for the treatment of established nausea and vomiting.
Sancuso (granisetron) transdermal	Sancuso (Granisetron Transdermal System) is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.
Sustol (granisetron extended-release) injection	Sustol is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.
Varubi (rolapitant) tablet	Varubi is indicated 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.

Product	FDA Approved Indication
Zofran (ondansetron) tablets, solution **Zofran ODT** (ondansetron) orally disintegrating tablets)	Zofran is indicated for the prevention of nausea and vomiting associated with: • highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m2 • initial and repeat courses of moderately emetogenic cancer chemotherapy • radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen Zofran is also indicated for the prevention of postoperative nausea and/or vomiting.
Zuplenz (ondansetron) film	**Prevention of Nausea and Vomiting Associated with Highly Emetogenic Cancer Chemotherapy** Zuplenz (ondansetron) oral soluble film is indicated for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2. **Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer** Chemotherapy Zuplenz is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. **Prevention of Nausea and Vomiting Associated with Radiotherapy** Zuplenz is indicated for the 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** Zuplenz is indicated for the prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, Zuplenz is recommended even where the incidence of postoperative nausea and/or vomiting is low.

Recommended Dosing

FDA Recommended Dosing

Product	FDA Recommended Dosing

Akynzeo (palonosetron/ fosnetupitant) capsule, injection

The recommended dosages of Akynzeo and dexamethasone in adults for the prevention of nausea and vomiting associated with administration of emetogenic chemotherapy are shown in Table 1.

Akynzeo capsules can be taken with or without food.

Table 1: Antiemetic Treatment Regimen

Treatment Regimen	Day 1		Days 2 to 4
Highly Emetogenic Chemotherapy, including Cisplatin-Based Chemotherapy			
Akynzeo capsules	1 capsule of Akynzeo	1 hour before chemotherapy	Dexamethasone 8 mg once a day
	Dexamethasone 12 mg	30 minutes before chemotherapy	
Akynzeo for injection	1 vial of Akynzeo	Infuse over 30 minutes starting 30 minutes before chemotherapy	Dexamethasone 8 mg once a day
	Dexamethasone 12 mg	30 minutes before chemotherapy	
Anthracyclines and Cyclophosphamide-Based Chemotherapy and Chemotherapy Not Considered Highly Emetogenic			
Akynzeo capsules	1 capsule of Akynzeo	1 hour before chemotherapy	None
	Dexamethasone 12 mg	30 minutes before chemotherapy	

Aloxi (palonosetron) injection

Chemotherapy-Induced Nausea and Vomiting

Age	Dose*	Infusion Time
Adults	**0.25 mg** x 1	Infuse over **30 seconds** beginning approx. 30 min before the start of chemo
Pediatrics (1 month to less than 17 years)	**20 micrograms per kilogram** (max 1.5 mg) x 1	Infuse over **15 minutes** beginning approx. 30 min before the start of chemo

*Note different dosing units in pediatrics

Postoperative Nausea and Vomiting
Dosage for Adults - a single 0.075 mg intravenous dose administered over 10 seconds immediately before the induction of anesthesia.

Anzemet (dolasetron) tablet

The recommended doses of Anzemet tablets should not be exceeded.

Adults
The recommended oral dosage of Anzemet (dolasetron mesylate) is 100 mg given within one hour before chemotherapy.

Pediatric Patients
The recommended oral dosage in pediatric patients 2 to 16 years of age is 1.8 mg/kg given within one hour before chemotherapy, up to a maximum of 100 mg. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

In children for whom 100 mg is not appropriate based on their weight or ability to swallow tablets, the Anzemet injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients. The diluted product may be kept up to 2 hours at room temperature before use. However, Anzemet injection solution when administered intravenously is contraindicated in adult and pediatric patients for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy due to dose dependent QT prolongation.

<table>
<tr><td></td><td>Use in the Elderly, Renal Failure Patients, or Hepatically Impaired Patients
No dosage adjustment is recommended, however; ECG monitoring is recommended for elderly and renally impaired patients.</td></tr>
<tr><td>Cinvanti
(aprepitant)
injectable
emulsion</td><td>Prevention of Nausea and Vomiting Associated with HEC and MEC
The recommended dosages in adults of Cinvanti, dexamethasone, and a 5-HT3 antagonist for the prevention of nausea and vomiting associated with administration of HEC or MEC are shown in Table 1 and Table 2, respectively. Administer Cinvanti intravenously either by injection over a two (2) minute period or by infusion over a thirty (30) minute period on Day 1, completing the injection or infusion approximately 30 minutes prior to chemotherapy.

Table 1. Recommended Dosage of Cinvanti for the Prevention of Nausea and Vomiting Associated with HEC (Single Dose Regimen)
<table>
<tr><th>Agent</th><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th></tr>
<tr><td>Cinvanti</td><td>130 mg intravenously</td><td>None</td><td>None</td><td>None</td></tr>
<tr><td>Dexamethasone[a]</td><td>12 mg orally</td><td>8 mg orally</td><td>8 mg orally twice daily</td><td>8 mg orally twice daily</td></tr>
<tr><td>5-HT$_3$</td><td>See selected 5-HT3 antagonist prescribing information for recommended dosage</td><td>None</td><td>None</td><td>None</td></tr>
</table>
[a] Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Also administer dexamethasone in the evenings on Days 3 and 4. A 50% dosage reduction of dexamethasone on Days 1 and 2 is recommended to account for a drug interaction with aprepitant.

Table 2. Recommended Dosage of Cinvanti for the Prevention of Nausea and Vomiting Associated with MEC (3-Day Regimen with Oral Aprepitant on Days 2 and 3)
<table>
<tr><th>Agent</th><th>Day 1</th><th>Day 2</th><th>Day 3</th></tr>
<tr><td>Cinvanti</td><td>100 mg intravenously</td><td>None</td><td>None</td></tr>
<tr><td>Oral Aprepitant</td><td>None</td><td>80 mg orally</td><td>80 mg orally</td></tr>
<tr><td>Dexamethasone[a]</td><td>12 mg orally</td><td>None</td><td>None</td></tr>
<tr><td>5-HT$_3$</td><td>See selected 5-HT3 antagonist prescribing information for recommended dosage</td><td>None</td><td>None</td></tr>
</table>
[a] Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with aprepitant.</td></tr>
<tr><td>Emend
(aprepitant)
capsule,
suspension</td><td>Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)
Adults and Pediatric Patients 12 Years of Age and Older
The recommended oral dosage of Emend capsules, dexamethasone, and a 5-HT3 antagonist in adults and pediatric patients 12 years of age and older who can swallow oral capsules, for the prevention of nausea and vomiting associated with administration of HEC or MEC is shown in Table 1 or Table 2, respectively. For patients who cannot swallow oral capsules, Emend for oral suspension can be used instead of Emend capsules as shown in Table 3.</td></tr>
</table>

Table 1: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with HEC

	Population	Day 1	Day 2	Day 3	Day 4
Emend capsules*	Adults and Pediatric Patients 12 Years and Older	125 mg orally	80 mg orally	80 mg orally	None
Dexamethasone	Adults	12 mg orally	8 mg orally	8 mg orally	8 mg orally
	Pediatric Patients 12 Years and Older	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4. †			
5-HT_3 antagonist	Adults and Pediatric Patients 12 Years and Older	See selected 5-HT3 antagonist prescribing information for recommended dosage	None	None	None

*Administer Emend capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer Emend capsules in the morning.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with Emend.

Table 2: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with MEC

	Population	Day 1	Day 2	Day 3
Emend capsules*	Adults and Pediatric Patients 12 Years and Older	125 mg orally	80 mg orally	80 mg orally
Dexamethasone	Adults	12 mg orally	None	None
	Pediatric Patients 12 Years and Older	If a corticosteroid, such as dexamethasone, is coadministered, administer 50% of the recommended corticosteroid dose on Days 1 through 4.†		
5-HT_3 antagonist	Adults and Pediatric Patients 12 Years and Older	See selected 5-HT3 antagonist prescribing information for recommended dosage	None	None

*Administer Emend capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer Emend capsules in the morning.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with Emend.

<u>Pediatric Patients 6 Months to less than 12 Years of Age or Pediatric and Adult Patients Unable to Swallow Capsules</u>
The recommended dose of Emend for oral suspension to be administered with a 5-HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of HEC or MEC is specified in Table 3. Dosing of Emend for

oral suspension is based on weight, to a maximum of 125 mg on Day 1 and 80 mg on Days 2 and 3. Dosing in pediatric patients less than 6 kg is not recommended.

Table 3: Recommended Dosing in Pediatric Patients 6 Months to Less than 12 Years of Age or Pediatric and Adult Patients Unable to Swallow Capsules

	Population	Day 1	Day 2	Day 3	Day 4
Emend for oral suspension*	Pediatric Patients 6 Months to Less than 12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	3 mg/kg orally Maximum dose 125 mg	2 mg/kg orally Maximum dose 80 mg	2 mg/kg orally Maximum dose 80 mg	None
Dexamethasone	Adults Unable to Swallow Capsules	See Table 1 or 2	See Table 1 or 2	See Table 1 or 2	See Table 1 or 2
	Pediatric Patients 6 Months to Less than 12 Years or Pediatric Patients Unable to Swallow Capsules	If a corticosteroid, such as dexamethasone, is coadministered, administer 50% of the recommended corticosteroid dose on Days 1 through 4.†			
5-HT_3 antagonist	Pediatric Patients 6 Months to Less than 12 Years or Pediatric Patients Unable to Swallow Capsules	See selected 5-HT3 antagonist prescribing information for recommended dosage	None	None	None

*After preparation, the final concentration of Emend for oral suspension is 25 mg/mL. Administer Emend for oral suspension 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer Emend for oral suspension in the morning.

†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with Emend.

Prevention of Postoperative Nausea and Vomiting (PONV)

The recommended oral dosage of Emend capsules in adults is 40 mg within 3 hours prior to induction of anesthesia.

Emend (fosaprepitant) injection

Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients
The recommended dosage of Emend for injection, dexamethasone, and a 5-HT3 antagonist for the prevention of nausea and vomiting associated with administration of HEC or MEC in adults is shown in Table 1 or Table 2, respectively. Administer Emend for injection as an intravenous infusion on Day 1 over 20 to 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.

Table 1: Recommended Adult Dosing for the Prevention of Nausea and Vomiting Associated with HEC

	Day 1	Day 2	Day 3	Day 4
Emend for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	None	None	None
Dexamethasone*	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	None	None	None

*Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Also administer dexamethasone in the evenings on Days 3 and 4. A 50% dosage reduction of dexamethasone on Days 1 and 2 is recommended to account for a drug interaction with Emend.

Table 2: Recommended Adult Dosing for the Prevention of Nausea and Vomiting Associated with MEC

	Day 1
Emend for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy
Dexamethasone*	12 mg orally
5-HT_3 antagonist	See selected 5-HT3 antagonist prescribing information for the recommended dosage

*Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with Emend.

Prevention of Nausea and Vomiting Associated with HEC and MEC in Pediatric Patients
The recommended pediatric dose regimens of Emend, to be administered with a 5-HT3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemotherapy regimens of HEC or MEC, are shown in Tables 3 and 4. Single-day chemotherapy regimens include those regimens in which HEC or MEC is administered for a single day only. Multi-day chemotherapy regimens include chemotherapy regimens in which HEC or MEC is administered for 2 or more days.

Emend Dosage Regimens for Use with Single-Day Chemotherapy Regimens

For pediatric patients weighing at least 6 kg receiving single-day HEC or MEC, Emend may be administered as:

- a single dose regimen of Emend for injection infused through a central venous catheter on Day 1, as shown in Table 3; or
- as a 3-day EMEND regimen consisting of EMEND for injection as an intravenous infusion through a central venous catheter on Day 1 and EMEND capsules or EMEND for oral suspension on Days 2 and 3, as shown in Table 4.

Administer EMEND for injection on Day 1 over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years), completing the infusion approximately 30 minutes prior to chemotherapy.

Table 3: Single Dose Regimen of Emend for injection for Pediatric Patients 6 Months* to 17 Years for the Prevention of Nausea and Vomiting Associated with Single-Day Regimens of HEC or MEC

Drug	Age	Regimen
Emend for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes
	2 Years to less than 12 Years	4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes
	6 Months to less than 2 Years	5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes
Dexamethasone†	6 Months to 17 Years	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 and 2.
5-HT_3 antagonist	6 Months to 17 Years	See selected 5-HT3 antagonist prescribing information for the recommended dosage

*Dosing in pediatric patients less than 6 kg is not recommended
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1

Emend Dosage Regimen for Use with Multi-Day Chemotherapy Regimens

For pediatric patients weighing at least 6 kg receiving multi-day regimens of HEC or MEC, administer Emend on Days 1, 2, and 3. Administer Emend for injection as an intravenous infusion through a central venous catheter on Day 1 and Emend capsules or Emend for oral suspension on Days 2 and 3, as shown in Table 4.

Administer Emend for injection on Day 1 over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years), completing the infusion approximately 30 minutes prior to chemotherapy.

Table 4: Pediatric Patients 6 Months* to 17 Years Recommended 3-Day Emend Dosage Regimen for Prevention of Nausea and Vomiting Associated with Single or Multi-day Regimens of HEC or MEC

Age Group	Drug	Day 1	Day 2	Day 3
12 Years to 17 Years	Emend for injection	115 mg intravenously over 30 minutes	--	--
	Emend capsules†	--	80 mg orally	80 mg orally

<table>
<tr><td></td><td>
<table>
<tr><td>6 Months to Less than 12 Years</td><td>Emend for injection</td><td>3 mg/kg (maximum dose 115 mg) intravenously over 60 minutes</td><td>--</td><td>--</td></tr>
<tr><td></td><td>Emend for oral suspension</td><td>--</td><td>2 mg/kg orally (maximum 80 mg)</td><td>2 mg/kg orally (maximum 80 mg)</td></tr>
<tr><td>6 Months to 17 Years</td><td>Dexamethasone‡</td><td colspan="3">If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4</td></tr>
<tr><td>6 Months to 17 Years</td><td>5-HT_3 antagonist</td><td colspan="3">See selected 5-HT3 antagonist prescribing information for the recommended dosage</td></tr>
</table>
Dosing in pediatric patients less than 6 kg is not recommended
†For patients 12 years to 17 years who cannot swallow oral capsules, Emend for oral suspension can be used instead.
‡Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1
</td></tr>
<tr><td>Sancuso (granisetron) transdermal</td><td>The transdermal system (patch) should be applied to clean, dry, intact healthy skin on the upper outer arm. Sancuso should not be placed on skin that is red, irritated, or damaged.

Each patch is packed in a pouch and should be applied directly after the pouch has been opened.

The patch should not be cut into pieces.

Adults
Apply a single patch to the upper outer arm a minimum of 24 hours before chemotherapy. The patch may be applied up to a maximum of 48 hours before chemotherapy as appropriate. Remove the patch a minimum of 24 hours after completion of chemotherapy. The patch can be worn for up to 7 days depending on the duration of the chemotherapy regimen.</td></tr>
<tr><td>Sustol (granisetron extended-release) injection</td><td>The recommended dosage of Sustol is 10 mg administered subcutaneously. Administer Sustol in combination with dexamethasone at least 30 minutes before the initiation of MEC or AC combination chemotherapy. Administer Sustol on Day 1 of chemotherapy and not more frequently than once every 7 days because of the extended-release properties of the formulation.

For patients receiving MEC, the recommended dexamethasone dosage is 8 mg intravenously on Day 1. For patients receiving AC combination chemotherapy regimens, the recommended dexamethasone dosage is 20 mg intravenously on Day 1, followed by 8 mg orally, twice a day, on Days 2, 3 and 4.

If Sustol is administered with an NK1 receptor antagonist, see the prescribing information of the NK1 receptor antagonist for the recommended dexamethasone dosage.</td></tr>
</table>

Varubi (rolapitant) tablet

The recommended dosage of Varubi tablets in adults in combination with a 5-HT3 receptor antagonist and dexamethasone for the prevention of nausea and vomiting with emetogenic cancer chemotherapy is shown in Table 1. There is no drug interaction between rolapitant and dexamethasone, so no dosage adjustment for dexamethasone is required. Administer a dexamethasone dose of 20 mg on Day 1.

Administer Varubi prior to the initiation of each chemotherapy cycle, but at no less than 2 week intervals.

Administer Varubi tablets without regards to meals.

Table 1: Recommended Dosing Regimen of Varubi Tablets

	Day 1	Day 2	Day 3	Day 4
Prevention of Nausea and Vomiting Associated with Cisplatin-Based Highly Emetogenic Cancer Chemotherapy				
Varubi	Administer orally within 2 hours prior to initiation of chemotherapy 180 mg orally as a single dose	None		
Dexamethasone	20 mg; 30 min prior to initiation of chemotherapy	8 mg twice daily	8 mg twice daily	8 mg twice daily
5-HT_3 receptor antagonist	See the prescribing information for the co-administered 5-HT3 receptor antagonist for appropriate dosing information.	None		
Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer Chemotherapy and Combinations of Anthracycline and Cyclophosphamide				
Varubi	Administer orally within 2 hours prior to initiation of chemotherapy 180 mg orally as a single dose	None		
Dexamethasone	20 mg; 30 min prior to initiation of chemotherapy	None		
5-HT_3 receptor antagonist	See the prescribing information for the co-administered 5-HT3 receptor antagonist for appropriate	See the prescribing information for the co-administered 5-HT3 receptor antagonist for appropriate dosing information.		

		dosing information.	

Zofran (ondansetron) tablets, solution

Zofran ODT (ondansetron) orally disintegrating tablets

The recommended dosage regimens for adult and pediatric patients are described in Table 1 and Table 2, respectively.

Corresponding doses of Zofran tablets, Zofran ODT® orally disintegrating tablets and Zofran oral solution may be used interchangeably.

Table 1: Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24-mg dose administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin greater than or equal to 50 mg/m^2.
Moderately Emetogenic Cancer Chemotherapy	8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.
Radiotherapy	For total body irradiation: 8 mg administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for each day radiotherapy is given.
Postoperative	16 mg administered 1 hour before induction of anesthesia.

Table 2: Pediatric Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Moderately Emetogenic Cancer Chemotherapy	12 to 17 years of age: 8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy. 4 to 11 years of age: 4 mg administered 30 minutes before the start of chemotherapy, with a subsequent 4-mg dose 4 and 8 hours after the first dose. Then administer 4 mg three times a day for 1 to 2 days after completion of chemotherapy.

Zuplenz (ondansetron) film

Prevention of Nausea and Vomiting Associated with Highly Emetogenic Cancer Chemotherapy

Adults

The recommended adult oral dosage of Zuplenz (ondansetron) oral soluble film is 24 mg given successively as three 8 mg films administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2. Each Zuplenz oral soluble film should be allowed to dissolve completely before administering the next film. Multiday, single-dose administration of a 24 mg dosage has not been studied.

	Pediatrics Safety and effectiveness of Zuplenz in pediatric patients have not been established for this indication. **Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer Chemotherapy** Adults The recommended adult oral dosage is one 8 mg Zuplenz oral soluble film given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8 mg Zuplenz oral soluble film should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy. Pediatrics For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4 mg Zuplenz oral soluble film given three times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4 mg Zuplenz oral soluble film should be administered three times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy. **Prevention of Nausea and Vomiting Associated with Radiotherapy** Adults The recommended adult oral dosage of Zuplenz oral soluble film is one 8 mg film given three times a day. For total body irradiation, one 8 mg Zuplenz oral soluble film should be administered 1 to 2 hours before each fraction of radiotherapy administered each day. For single high-dose fraction radiotherapy to the abdomen, one 8 mg Zuplenz oral soluble film should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen, one 8 mg Zuplenz oral soluble film should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given. Pediatrics Safety and effectiveness of Zuplenz in pediatric patients have not been established for this indication. **Prevention of Postoperative Nausea and/or Vomiting** Adults The recommended adult oral dosage of Zuplenz oral soluble film is 16 mg given successively as two 8 mg films 1 hour before induction of anesthesia. Each Zuplenz oral soluble film should be allowed to dissolve completely before administering the next film. Pediatrics Safety and effectiveness of Zuplenz in pediatric patients have not been established for this indication.

Drug Availability

Product	Drug Availability
Akynzeo (palonosetron/ fosnetupitant) capsule	Supplied as capsules containing 300 mg netupitant/0.5 mg palonosetron.
Akynzeo	Supplied for injection containing 235 mg fosnetupitant/0.25 mg palonosetron.

Product	Drug Availability
(palonosetron/ fosnetupitant) injection	
Aloxi (palonosetron) injection	Supplied for injection as a single-use vial containing either 0.25 mg (free base) per 5 mL or 0.075 mg (free base) per 1.5 mL.
Anzemet (dolasetron) tablet	Supplied as tablets containing 50 mg dolasetron.
Cinvanti (aprepitant) injectable emulsion	Supplied for injection as a single-use vial containing 130 mg/18 mL (7.2 mg/mL) aprepitant.
Emend (aprepitant) capsule, suspension	Supplied as capsules containing 125 mg, 80 mg, 40 mg capsules, or as a unit-of-use tripack containing one 125-mg capsule and two 80-mg capsules of aprepitant. Also supplied as powder for oral suspension in a single-use pouch containing 125 mg aprepitant.
Emend (fosaprepitant) injection	Supplied for injection as a single-dose vial for reconstitution containing 150 mg fosaprepitant.
Sancuso (granisetron) transdermal	Supplied as a 52 cm^2 patch containing 34.3 mg of granisetron.
Sustol (granisetron extended-release) injection	Supplied as an extended-release injection containing 10 mg/0.4 mL granisetron in a single-dose prefilled syringe.
Varubi (rolapitant) tablet	Supplied as tablets containing 90 mg rolapitant.
Zofran (ondansetron) tablets, solution **Zofran ODT** (ondansetron) orally disintegrating tablets	Supplied as tablets containing 4 mg, 8 mg ondansetron. Supplied as orally disintegrating tablets containing 4 mg, 8 mg ondansetron. Supplied as oral solution containing 4 mg/5 mL ondansetron.
Zuplenz (ondansetron) film	Supplied as an oral soluble film containing 4 mg, 8 mg ondansetron.

General Background

Pharmacology

Aprepitant (Emend, Cinvanti), fosaprepitant (Emend), and rolapitant (Varubi) are a substance P/neurokinin 1 (NK1) receptor antagonists. Palonosetron (Aloxi), granisetron (Sustol) are selective serotonin-3 (5-HT3) receptor antagonists. Akynzeo is a combination product of a 5-HT3 receptor antagonist (palonosetron) and an NK1 receptor antagonist (netupitant).

Professional Societies/Organizations

National Comprehensive Cancer Network (NCCN) provides recommendations for antiemetic therapy regimens based on the emetogenic risk of the chemotherapy and if it is intravenous or oral. The emetogenic risk of intravenous antineoplastics is based on the frequency of emesis. High emetic risk agents have a greater than 90% frequency of emesis (an example includes combination regimens that contain an anthracycline and cyclophosphamide). Moderate emetic risk has a 30-90% frequency of emesis while low emetic risk and minimal emetic risk have a 10-30% and less than 10% frequency of emesis, respectively. For oral antineoplastic agents, the levels are divided into those with moderate to high emetic risk (greater than or equal to 30% frequency of emesis) and minimal to low emetic risk (less than 30% frequency of emesis). (NCCN, 2019)

For high emetic risk intravenous (IV) chemotherapy, NCCN recommends several options for acute and delayed emesis prevention without a preference given to one regimen over another. Regimens recommended include either aprepitant oral or IV, fosaprepitant IV, or rolapitant oral in combination with a 5-HT3 receptor antagonist (palonosetron IV; granisetron subcutaneous [SQ], oral, IV or transdermal; or ondansetron oral or IV) with dexamethasone. Other options include netupitant/palonosetron oral in combination with dexamethasone; olanzapine oral with palonosetron IV and dexamethasone; or aprepitant oral or fosaprepitant IV in combination with a 5-HT3 receptor antagonist, dexamethasone, and olanzapine. (NCCN, 2019)

For moderate emetic risk IV chemotherapy, several options are recommended without preference for acute and delayed emesis prevention. One option recommends a 5-HT3 receptor antagonist in combination with dexamethasone. NCCN notes a preference for palonosetron IV or granisetron SQ when a 5-HT3 receptor antagonist is not used in combination with an NK1 antagonist. Other options include use of aprepitant oral or IV, fosaprepitant IV, rolapitant oral in combination with a 5-HT3 receptor antagonist and dexamethasone; netupitant/palonosetron oral in combination with dexamethasone; or olanzapine oral with palonosetron IV and dexamethasone. (NCCN, 2019)

Emesis prevention for low emetic risk IV chemotherapy includes use of dexamethasone; metoclopramide; prochlorperazine; or an oral 5-HT3 receptor antagonist. There is not routine prophylaxis recommended for minimal emetic risk IV chemotherapy. (NCCN, 2019)

For emesis prevention with oral chemotherapy, NCCN recommends a 5-HT3 receptor antagonist granisetron oral or transdermal; or ondansetron oral) for high to moderate emetic risk therapy. As needed treatment is recommended initially for low to minimal emetic risk with recommendations provided when nausea/vomiting is experienced. (NCCN, 2019)

If breakthrough chemotherapy-induced nausea and vomiting occurs, recommendations for subsequent chemotherapy cycles include changing the antiemetic regimen to a higher level for primary treatment. (NCCN, 2019)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

In a Choosing Wisely statement, American Society of Clinical Oncology (ASCO) does not recommend individuals on a chemotherapy regimen with low or moderate risk of causing nausea and vomiting be started on antiemetic drugs intended for use with a regiment that has a high risk of causing nausea and vomiting. (Choosing Wisely, 2013)

Off Label Uses

AHFS Drug Information 2019 Edition does not support any off-label uses of aprepitant, fosaprepitant, granisetron, palonosetron, palonosetron/fosnetupitant, or rolapitant.

Coding/Billing Information

Note: Akynzeo® (palonosetron/netupitant capsules), Emend® (aprepitant capsules, suspension), Sancuso® (granisetron transdermal), and Varubi® (rolapitant tablets) are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions. The following drugs require medical drug coding and are listed as follows:

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0185	Injection, aprepitant, 1 mg
J1453	Injection, fosaprepitant, 1 mg
J1454	Injection, fosnetupitant 235 mg and palonosetron 0.25 mg
J1627	Injection, granisetron, extended-release, 0.1 mg
J2469	Injection, palonosetron HCl, 25 mcg

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