Antiemetic Medical Policy Prior Authorization Program Summary

Precertification/Prior Authorization may be required under certain plans. Please verify each member's benefits.

OBJECTIVE
The intent of the Antiemetic medical drug criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and to verify appropriate FDA labeled dosing for specified indications. The criteria will direct its use to the FDA approved and/or clinically supported indications. Criteria requires that patients do not have any FDA labeled contraindications to use with the requested agent and that the agent(s) be used for highly to moderately emetogenic risk chemotherapy regimens. The program will approve the requested agent for doses within FDA labeling. Doses above FDA labeling will be approved when the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

Target Agents
Akynzeo® for injection (fosnetupitant and palonosetron)
Aloxi® (palonosetron)[a]
Cinvanti™ (aprepitant)
Emend IV® (fosaprepitant)
Palonosetron (palonosetron hydrochloride)
Sustol® (granisetron)
Varubi IV® (rolapitant)
a – generic available

Evaluation
The requested agent will be approved when ALL of the following are met:
1. The patient does not have any FDA labeled contraindications to the requested agent
   AND
2. The patient will be receiving **ONE** of the following:
   a. High risk* emetogenic chemotherapy regimen
      OR
   b. Moderate risk* emetogenic chemotherapy regimen
   AND
3. ONE of the following:
   a. The dose is within the FDA labeled dose
      OR
   b. The dose requested is greater than the maximum dose recommended in FDA labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

*High, moderate, low and minimal risk chemotherapy regimens are available from NCCN at: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.

Length of Approval: For oncology diagnosis: for the approval duration assigned through Oncology Select review process, not to exceed 12 months.
For non-oncology diagnosis: up to 12 months.

Agent	Contraindication(s)
Akynzeo (fosnetupitant and palonosetron)	None
Aloxi (palonosetron)	Hypersensitivity to Aloxi or any of its components
Cinvanti (aprepitant)	Known hypersensitivity to any component of this drug Concurrent use with pimozide
Emend IV (fosaprepitant)	• Known hypersensitivity to any component of this drug • Concurrent use with pimozide
Sustol (granisetron)	Hypersensitivity to granisetron, any of the components of Sustol, or to any of the other 5-HT3 receptor antagonists
Varubi (rolapitant)	Patients taking CYP2D6 substrates with a narrow therapeutic index, such as thioridazine and pimozide. Varubi can significantly increase the plasma concentrations of thioridazine and pimozide, which may result in QT prolongation and Torsades de Pointes

FDA APPROVED INDICATIONS AND DOSAGE[1,4-9]

Agent	Indication	Dosing
Akynzeo® (fosnetupitant and palonosetron)	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	One vial reconstituted in 50 mL of 5% dextrose injection USP, or 0.9% sodium chloride injection USP and administered as a 30 minute infusion starting approximately 30 minutes prior to the start of chemotherapy
Aloxi® (palonosetron)[#]	Moderately emetogenic cancer chemotherapy: prevention of acute and delayed nausea and vomiting associated with initial and repeat courses	0.25 mg intravenously 30 minutes prior to initial chemotherapy dose. May be used for initial and repeat cycles.
	Highly emetogenic cancer chemotherapy: prevention of acute nausea and vomiting associated with initial and repeat courses	0.25 mg intravenously 30 minutes prior to initial chemotherapy dose. May be used for initial and repeat cycles.
	Pediatrics 1 month- 17 years: Prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy	20 mcg/kg (max of 1.5 mg) x 1 intravenously 30 minutes prior to initial chemotherapy dose. May be used for initial and repeat cycles
Cinvanti™ (aprepitant)	Indicated in adults, in combination with other antiemetic agents, for the prevention of: • acute and delayed nausea 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)	HEC (single dose regimen): 130 mg on day 1 as an intravenous infusion 30 minutes prior to chemotherapy MEC (3-day regimen): 100 mg on day 1 as an intravenous infusion 30 minutes prior to chemotherapy. Aprepitant capsules (80mg) are given orally on days 2 and 3
Emend® IV (fosaprepitant)	Indicated in adults, in combination with other antiemetic agents (dexamethasone and a 5-HT3 antagonists), 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)	Recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
Palonosetron (palonosetron hydrochloride)	• Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy • Prevention of acute nausea and	**Chemotherapy-induced nausea and Vomiting:** 0.25 mg IV over 30 seconds approximately 30 minutes before the start of chemotherapy

	vomiting associated with highly emetogenic cancer chemotherapy ● Prevention of postoperative nausea and vomiting	**Postoperative nausea and vomiting:** 0.075 mg IV over 10 seconds immediately before the induction of anesthesia
Sustol® (granisetron)	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.	The recommended dosage is 10 mg administered subcutaneously. Administer in combination with dexamethasone at least 30 minutes before the initiation of MEC or AC combination chemotherapy. Administer 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.
Varubi®(rolapitant)	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.	Infuse 166.5mg intravenously over 30 minutes within 2 hours prior to initiation of chemotherapy on Day 1.

Aloxi is also indicated for prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery; however, in this situation, the use of Aloxi is infused immediately before induction of anesthesia and would most likely be part of the hospital bill and is not included in this particular criteria.

Aloxi (palonosetron) is antiemetic and antinauseant agent. It is a serotonin subtype 3 (5-HT_3) receptor antagonist with little affinity for other 5-HT receptors. The main use of this agent is prevention of nausea and vomiting associated with moderate to high risk cancer chemotherapy regimens. The 5-HT_3 receptors are located on the nerve terminals of vagus nerve in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. Chemotherapeutic agents are thought to release serotonin from the enterochromaffin cells of the small intestine which then activates 5-HT_3 receptors on the afferent vagal nerve and induces the vomiting reflex.[1]

Aloxi is contraindicated in patients with a hypersensitivity to the agent or any of its components. Hypersensitivity including anaphylaxis has been reported with the use of this agent. The most common adverse events occurring in ≥5% of patients include headache and constipation.[1]

Emend (fosaprepitant) is a prodrug of aprepitant. Aprepitant is a selective, high-affinity antagonist of human substance P/neurokinin 1 (NK_1) and is responsible for Emend's antiemetic properties. It has little

to no affinity for 5-HT_3, dopamine, and corticosteroid receptors. Aprepitant crosses the blood brain barrier and is believed to work centrally to inhibit acute and delayed emesis.[4]

Emend is contraindicated in patients who are hypersensitive to any component of Emend and contraindicated while concomitantly taking pimozide. Aprepitant inhibits CYP3A4, which could cause an elevation in pimozide and could subsequently cause serious or life-threatening reactions (e.g. QT prolongation).[4]

Sustol (granisetron) is a selective 5-hydroxytryptamine3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT1, 5-HT1A, 5-HT1B/C, 5-HT2; for alpha1-, alpha2-, or beta-adrenoreceptors; for dopamine-D2; or for histamine-H1; benzodiazepine; picrotoxin or opioid receptors.[5]

Sustol is contraindicated in patients with hypersensitivity to granisetron, any of the components of Sustol, or to any of the other 5-HT3 receptor antagonists.[5]

Varubi (rolapitant) is a selective and competitive antagonist of human substance P/NK1 receptors. It does not have significant affinity for the NK2 or NK3 receptors or for a battery of other receptors, transporters, enzymes and ion channels.[6]

Varubi is contraindicated in patients taking CYP2D6 substrates with a narrow therapeutic index, such as thioridazine and pimozide. It can significantly increase the plasma concentrations of thioridazine and pimozide, which may result in QT prolongation and Torsades de Pointes.[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.[2]

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.[2]

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.[2]

There are several identified classes of chemotherapy-induced N/V 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).[2]

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 N/V. 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.[2]

References

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3. Deleted.
4. Emend for injection prescribing information. Merck & Co., Inc. February 2016. https://www.merck.com/product/usa/pi_circulars/e/emend_iv/emend_iv_pi.pdf. Accessed on 5/8/17.
5. Sustol prescribing information. Heron Therapeutics. November 2016.
6. Varubi prescribing information. Tesaro. October 2017.
7. Cinvanti prescribing information. Heron Therapeutics. November 2017.
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