Corporate Medical Policy: Antiemetic Injection Therapy **"Notification"** **POLICY EFFECTIVE APRIL 1, 2026**

Restricted Product(s):

- fosnetupitant/palonosetron (Akynzeo®) intravenous infusion for administration by a healthcare professional
- palonosetron (Posfrea™) intravenous infusion for administration by a healthcare professional
- aprepitant (Cinvanti®) intravenous injection or infusion for administration by a healthcare professional
- fosaprepitant (Focinvez™) intravenous infusion for administration by a healthcare professional
- granisetron (Sustol®) extended-release subcutaneous injection for administration by a healthcare professional

Preferred Product(s) (Unrestricted)	Non-Preferred Product(s)
5-Hydroxytryptamine Receptor Antagonist (5HT3 RA)	
Aloxi (palonosetron) injection (J2469) Anzemet (dolasetron mesylate) tablets* Kytril (granisetron) injection, tablets* Zofran (ondansetron) injection, tablets*	Sustol (granisetron extended release) injection (J1627) Posfrea (palonosetron) injection (J2468)
Neurokinin 1 Receptor Antagonist (NK1 RA)	
Emend (aprepitant) capsules* Emend (fosaprepitant) injection (J1453) Fosaprepitant (teva) injection (J1456) Varubi (rolapitant) tablets*	Cinvanti (aprepitant) injection (J0185) Focinvez (fosaprepitant) injection (J1434)
NK1 RA/5HT3 RA Combination	
Akynzeo (netupitant/palonosetron) capsule*	Akynzeo (fosnetupitant/palonosetron) injection (J1454)

*Pharmacy benefit drug. Formulary restrictions may apply.

FDA Approved Use:

- Fosnetupitant/palonosetron (Akynzeo®)
  - For use in combination with dexamethasone, in adults, for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
  - Limitations of use: Not for prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy

- Palonosetron (Posfrea™)
  - For prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
  - For prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC)
- Aprepitant (Cinvanti®)
  - For use in combination with other antiemetic agents, in adults, for prevention of:
    - Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin as a single-dose regimen
    - Delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen
    - Nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen
  - Limitations of use: Not for treatment of established nausea and vomiting
- Fosaprepitant (Focinvez™)
  - For use in combination with other antiemetic agents, in adults and pediatric patients 6 months of age and older, for 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: Not for treatment of established nausea and vomiting
- Granisetron (Sustol®)
  - For use in combination with other antiemetics, in adults, for 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

**NOTE: This policy only addresses antiemetic injectable medications when used to prevent nausea and vomiting caused by cancer chemotherapy. Any non-oncologic FDA labeled or compendia supported uses for the above restricted products are not addressed in this policy and may be addressed elsewhere.

NOTE: Use of injectable/intravenous Anzemet® (dolasetron mesylate) is considered **investigational for the prevention and/or treatment of acute and delayed nausea and vomiting related to use of any cancer chemotherapy agent(s). BCBSNC does not provide coverage for investigational services or procedures.

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

1. The request is for **Akynzeo (fosnetupitant and palonosetron)**; **AND**
    a. The patient is 18 years of age or older; **AND**
    b. The requested agent is being prescribed in combination with dexamethasone, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and/or moderately emetogenic cancer chemotherapy; **AND**
        i. There is documented use of a highly and/or moderately emetogenic cancer chemotherapy agent(s) listed in the most recent NCCN Guidelines (refer to guidelines beginning on page 7); **AND**
    c. ONE of the following:
        i. The patient has experienced a therapeutic failure or inadequate response to fosaprepitant (Emend); **OR**
        ii. The patient has a contraindication to fosaprepitant (Emend); **AND**
    d. ONE of the following:
        i. The patient has experienced a therapeutic failure or inadequate response to oral or intravenous granisetron OR oral or intravenous ondansetron; **OR**
        ii. The patient has experienced a therapeutic failure or inadequate response to generic palonosetron (Aloxi); **OR**
        iii. The patient has a contraindication to oral or intravenous granisetron, oral or intravenous ondansetron, AND generic palonosetron (Aloxi); **OR**

2. The request is for **Posfrea (palonosetron)**; **AND**
    a. The patient is 17 years of age or older; **AND**
    b. The requested agent is being prescribed for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and/or moderately emetogenic cancer chemotherapy; **AND**
        i. There is documented use of a highly and/or moderately emetogenic cancer chemotherapy agent(s) listed in the most recent NCCN Guidelines (refer to guidelines beginning on page 7); **AND**
    c. ONE of the following:
        i. The patient has experienced a therapeutic failure or inadequate response to generic palonosetron (Aloxi); **OR**
        ii. The patient has a contraindication to generic palonosetron (Aloxi); **OR**

3. The request is for **Cinvanti (aprepitant)**; **AND**
    a. The patient is 18 years of age or older; **AND**
    b. The requested agent is being prescribed in combination with other antiemetic agents (i.e., 5-HT_3 antagonist [e.g., granisetron, ondansetron, palonosetron] and corticosteroid [i.e., dexamethasone]), for the prevention of acute and delayed nausea and vomiting

associated with initial and repeat courses of highly and/or moderately emetogenic cancer chemotherapy, including high-dose cisplatin; **AND**
    i. There is documented use of a highly and/or moderately emetogenic cancer chemotherapy agent(s) listed in the most recent NCCN Guidelines (refer to guidelines beginning on page 7); **AND**
c. ONE of the following:
    i. The patient has experienced a therapeutic failure or inadequate response to fosaprepitant (Emend); **OR**
    ii. The patient has a contraindication to fosaprepitant (Emend); **OR**

4. The request is for **Focinvez (fosaprepitant)**; **AND**
    a. The patient is 6 months of age or older and weighs at least 6 kg; **AND**
    b. The requested agent is being prescribed in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and/or moderately emetogenic cancer chemotherapy, including high-dose cisplatin; **AND**
        i. There is documented use of a highly and/or moderately emetogenic cancer chemotherapy agent(s) listed in the most recent NCCN Guidelines (refer to guidelines beginning on page 7); **AND**
    c. ONE of the following:
        i. The patient has experienced a therapeutic failure or inadequate response to fosaprepitant (Emend); **OR**
        ii. The patient has a contraindication to fosaprepitant (Emend); **OR**

5. The request is for **Sustol (granisetron)**; **AND**
    a. The patient is 18 years of age or older; **AND**
    b. The requested agent is being prescribed in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens; **AND**
        i. There is documented use of a moderately emetogenic cancer chemotherapy agent(s) listed in the most recent NCCN Guidelines (refer to guidelines beginning on page 7) OR documented use of an anthracycline and cyclophosphamide (AC) combination chemotherapy regimen; **AND**
    c. ONE of the following:
        i. The patient has experienced a therapeutic failure or inadequate response to oral or intravenous granisetron OR oral or intravenous ondansetron; **OR**
        ii. The patient has experienced a therapeutic failure or inadequate response to generic palonosetron (Aloxi); **OR**
        iii. The patient has a contraindication to oral or intravenous granisetron, oral or intravenous ondansetron, AND generic palonosetron (Aloxi); **OR**

6. The requested quantity (dose) and treatment duration (and maximum units) is within FDA labeled dosing for the requested indication or NCCN 1 or 2A compendia supported dosing for the requested indication.

   Duration of Approval: 365 days (1 year)

NOTE:
Use of antiemetic injection therapy may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of **cancer** either:

1. In accordance with FDA label (when clinical benefit has been established, and it is not determined to be investigational as defined in the Blue Cross NC Corporate Medical Policy (CMP), "Investigational (Experimental) Services." [please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia]; **OR**
2. In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

FDA Label Reference			
Medication	**Indication**	**Dosing**	**HCPCS**
fosnetupitant/palonosetron (Akynzeo®) intravenous (IV) infusion	Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy	IV: One vial (235 mg fosnetupitant/0.25 mg palonosetron) 30 minutes before chemotherapy	J1454
palonosetron (Posfrea™) intravenous (IV) infusion	Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy	IV: • Adults: 0.25 **mg** as a single dose 30 minutes before chemotherapy	J2468

FDA Label Reference			
Medication	**Indication**	**Dosing**	**HCPCS**
aprepitant (Cinvanti®) intravenous (IV) injection or infusion	Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy	IV: • HEC and MEC (single-dose regimen): 130 mg on Day 1, 30 minutes before chemotherapy • MEC (3-day regimen): 100 mg on Day 1, 30 minutes before chemotherapy. Aprepitant capsules (80 mg) are then given by mouth on Days 2 and 3. • Used as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist	J0185
fosaprepitant (Focinvez™) intravenous (IV) infusion	Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy	IV: • Adults: 150 mg on Day 1, 30 minutes before chemotherapy • Pediatric patients (6 months to 17 years, Wt ≥ 6 kg): See package labeling	J1434
granisetron (Sustol®) extended-release subcutaneous (SC) injection	Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy	SC: 10 mg as a single injection at least 30 minutes before chemotherapy on Day 1. Do not administer more frequently than once every 7 days.	J1627

***Oncology-specific HCPCS codes: S0353, S0354

Other codes that may be applicable to this policy:

Diagnoses (ICD-10 codes) that are subject to medical necessity review: C00.0-C49.9, C4A.0-C4A.9, C50.011-C79.9, C7A.00-C7A.8, C7B.00-C7B.8, C80.0-C86.6, C88.2-C96.Z, D00.00-D09.9, D47.01, D47.02, D47.09, Z51.11, Z51.12

NCCN Guidelines Version 2.2025 Antiemesis - Emetogenic Potential of Parental Anticancer Agents			
High emetic risk (>90% frequency of emesis)	• AC combination (anthracycline and cyclophosphamide containing regimen) • Carboplatin AUC ≥4 • Carmustine >250 mg/m² • Cisplatin	• Cyclophosphamide >1500 mg/m² • Dacarbazine • Datopotamab deruxtecan-dlnk • Doxorubicin ≥60 mg/m² • Epirubicin >90 mg/m² • Fam-trastuzumab deruxtecan-nxki	• Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Melphalan ≥140 mg/m² • Sacituzumab govitecan-hziy • Streptozocin • Zolbetuximab-clzb
Moderate emetic risk (>30%–90% frequency of emesis)	• Aldesleukin >12–15 million IU/m² or 600,000 IU/kg • Amifostine >300 mg/m² • Bendamustine • Busulfan • Carboplatin AUC <4 • Carmustine ≤250 mg/m² • Clofarabine • Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m²	• Dactinomycin • Daunorubicin • Dinutuximab • Doxorubicin <60 mg/m² • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Epirubicin ≤90 mg/m² • Idarubicin • Ifosfamide ≤2 g/m² per dose • Irinotecan	• Irinotecan (liposomal) • Lurbinectedin • Melphalan <140 mg/m² • Methotrexate ≥250 mg/m² • Metrivuximab soravtansine-gynx • Naxitamab-ggqk • Oxaliplatin • Romidepsin • Temozolomide • Trabectedin
Low emetic risk (10%–30% frequency of emesis)	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Amivantamab-vmjw • Arsenic trioxide • Axicabtagene ciloleucel • Azacitidine • Belinostat • Brentuximab vedotin • Brexucabtagene autoleucel • Cabazitaxel • Carfilzomib • Ciltacabtagene autoleucel • Copanlisib • Cytarabine (low dose) 100–200 mg/m²	• Elranatamab-bcmm • Epirubicin • Epoprostenol • Etoposide • Eribulin • Floxuridine • Fluorouracil (5-FU) • Gemtuzumab ozogamicin • Idecabtagene vicleucel • Inotuzumab ozogamicin • Isatuximab-irfc • Ixabepilone • Lifileucel • Lisocabtagene maraleucel • Lisocabtagene maraleucel • Loncastuximab tesirine-lypl	• Mitoxantrone • Mosunetuzumab-axgb • Necitumumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Polatuzumab vedotin-piiq • Pralatrexate • Talimogene laherparevec • Tisotumab vedotin-tftv • Topotecan • Trastuzumab • Trastuzumab deruxtecan • Ziv-aflibercept

NCCN Guidelines Version 2.2025 Antiemesis - Emetogenic Potential of Parental Anticancer Agents			
	• Docetaxel • Doxorubicin (liposomal) • Enfortumab vedotin-ejfv	• Methotrexate >50 - <250 mg/m² • Mitomycin pyelocalyceal solution	
Minimal emetic risk (<10% frequency of emesis)	• Alemtuzumab • Asparaginaseg • Atezolizumab • Atezolizumab and hyaluronidase • Avapritinib • Belantamab mafodotin • Bevacizumab • Bleomycin • Blinatumomab • Bortezomib • Cemiplimab-rwlc • Cetuximab • Cytarabine <100 mg/m² • Daratumumab • Daratumumab and hyaluronidase • Decitabine • Degarelix • Dexrazoxane • Dostarlimab-gxly	• Durvalumab • Elotuzumab • Fludarabine • Fulvestrant • Goserelin • Ipilimumab • Lanreotide • Leuprolide • Luspatercept-aamt • Magrolimab-cmbk • Methotrexate ≤50 mg/m² • Nelarabine • Nivolumab • Nivolumab and hyaluronidase • Nivolumab/relatlimab-rmbw • Obinutuzumab • Ofatumumab • Panitumumab • Pembrolizumab	• Pertuzumab • Pertuzumab/trastuzumab and hyaluronidase • Ramucirumab • Rituximab • Rituximab and hyaluronidase • Sirolimus-albumin • Talquetamab-tgvs • Tisagenlecleucel • Tislelizumab • Trastuzumab • Trastuzumab and hyaluronidase • Triptorelin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

NCCN Guidelines Version 2.2025 Antiemesis - Emetogenic Potential of Oral Anticancer Agents			
Moderate to high emetic risk (≥30% frequency of emesis): Prophylaxis required on days of PO anticancer agent administration	• Azacitidine • Busulfan ≥4 mg/day • Ceritinib • Cyclophosphamide ≥100 mg/m²/day	• Fedratinib • Lomustine (single day) • Midostaurin • Mitotane	• Selinexor • Temozolomide >75 mg/m²/day • Temozolomide ≤75 mg/m²/day with concurrent RT

NCCN Guidelines Version 2.2025 Antiemesis - Emetogenic Potential of Oral Anticancer Agents			
Moderate to high emetic risk (≥30% frequency of emesis): As needed (PRN) dosing is initially appropriate on days of PO anticancer agent administration	• Abemaciclib • Adagrasib • Avapritinib • Binimetinib • Bosutinib >400 mg/day • Cabozantinib • Crizotinib	• Dabrafenib • Elacestrant • Enasidenib • Encorafenib • Estramustine • Etoposide • Imatinib >400 mg/day	• Lenvatinib >12 mg/day • Niraparib • Olaparib • Procarbazine • Rucaparib • Tovorafenib • Trifluridine/tipiracil
Minimal to low emetic risk (<30% frequency of emesis)	• Abiraterone • Acalabrutinib • Afatinib • Alectinib • Alpelisib • Anastrozole • Apalutamide • Asciminib • Axitinib • Bezuftan • Bexarotene • Bicalutamide • Bosutinib ≤400 mg/day • Brigatinib • Busulfan <4 mg/day • Capecitabine • Capmatinib • Chlorambucil • Cobimetinib • Cyclophosphamide <100 mg/m²/day • Dacomitinib • Darolutamide • Dasatinib	• Fludarabine • Flutamide • Fruquintinib • Futibatinib • Gefitinib • Gilteritinib • Glasdegib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib ≤400 mg/day • Ivosidenib • Ixazomib • Lapatinib • Larotrectinib • Lenalidomide • Lenvatinib ≤12 mg/day • Lorlatinib • Megestrol • Melphalan • Mercaptopurine • Methotrexate • Momelotinib • Nilotinib	• Pralsetinib • Quizartinib • Regorafenib • Relugolix • Ripretinib • Ribociclib • Ruxolitinib • Selpercatinib • Sonidegib • Sorafenib • Sotorasib • Sunitinib • Talazoparib tosylate • Tamoxifen • Tazemetostat • Temozolomide ≤75 mg/m²/day • Tepotinib • Thalidomide • Thioguanine • Tivozanib • Topotecan • Toremifene • Trametinib • Tretinoin

NCCN Guidelines Version 2.2025 Antiemesis - Emetogenic Potential of Oral Anticancer Agents			
	• Decitabine and cedazuridine • Duvelisib • Eflornithine • Entrectinib • Enzalutamide • Erdafitinib • Erlotinib • Everolimus • Exemestane	• Niragacestat • Olutasidenib • Osimertinib • Pacritinib • Palbociclib • Pazopanib • Pemetrexed • Pexidartinib • Ponatinib	• Tucatinib • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat • Zanubrutinib

References: all information referenced is from FDA package insert unless otherwise noted below.

1. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2017;35(28):3240-3261.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Guidelines for Supportive Care. Antiemesis. Version 1.2024. Fort Washington, PA: NCCN, 12/13/23. Available at: http://www.nccn.org/. Accessed January 2024.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q3 annually.

April 2026: Criteria change: For Akynzeo, added trial and failure of generic palonosetron (Aloxi) as an option to existing required trial and failure of granisetron or ondansetron (oral or IV), or presence of contraindication to granisetron, ondansetron, and generic palonosetron (Aloxi). For Posfrea, added required trial and failure of generic palonosetron (Aloxi). For Focinvez, added required trial and failure of fosaprepitant (Emend). For Sustol, added required trial and failure of granisetron (oral or IV) OR ondansetron (oral or IV) OR generic palonosetron (Aloxi). Removed generic palonosetron (Aloxi) [J2469] and fosaprepitant (Emend) [J1453] from restricted products in policy (now unrestricted). Removed low/minimally emetogenic cancer chemotherapy antiemetic trial and failure requirements where present throughout policy according to FDA labeled use of restricted products. Other minor updates and formatting adjustments made throughout policy for clarity. **Policy notification given 1/1/2026 for effective date 4/1/2026**.
April 2025: Coding update: Adjusted formatting of policy to differentiate between palonosetron (Aloxi) and palonosetron (Posfrea) for clarity according to updated coding definition of HCPCS code J2468 to palonosetron hydrochloride (posfrea) on 1/1/2025.
July 2024: Coding change: Added HCPCS code J2468 (avyxa) for generic palonosetron to dosing reference table effective 7/1/2024.

April 2024: Coding change: Added HCPCS code J1434 for Focinvez to dosing reference table effective 4/1/2024; deleted C9399, J3490, J3590, and J9999 termed 3/31/2024.
April 2024: Criteria change: Added newly approved Focinvez (fosaprepitant) to policy, and associated dosing and HCPCS codes C9399, J3490, J3590, and J9999 to FDA label reference table. Adjusted trial and failure requirements for Cinvanti to require trial of Emend (fosaprepitant), and trial of granisetron or ondansetron for low to minimally emetogenic cancer chemotherapy regimens. Adjusted indication for Emend per FDA label to include pediatric patients 6 months of age or older weighing at least 6 kg. Updated NCCN Emetogenic Potential of Intravenous and Oral Antineoplastic Agents tables. Medical policy formatting change. **Policy notification given 1/29/2024 for effective date 4/1/2024**.
*Further historical criteria changes and updates available upon request from Medical Policy and/or Corporate Pharmacy.