Antiemetic injectable medications covered in this policy include Aloxi® (palonosetron HCl), Emend® (fosaprepitant dimeglumine), Anzemet® (dolasetron mesylate), Varubi® (rolapitant), Cinvanti™ (aprepitant), Sustol® (granisetron), and Akynzeo® (fosnetupitant and palonosetron). This policy addresses antiemetic injectable medications used to prevent nausea and vomiting caused by cancer chemotherapy.

Antiemetic injectable medications are used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, pregnancy, and surgery. Antiemetics work by blocking the action of serotonin, a natural substance that may cause nausea and vomiting, or by blocking the action of neurokinin, a natural substance in the brain that causes nausea and vomiting.

Selective serotonin 5-HT₃ receptor antagonists, Aloxi, Anzemet and Sustol, work by blocking serotonin binding at vagal afferents in the gut and in regions of the central nervous system (CNS) involved in emesis.

Substance P/neurokinin 1 (NK₁) receptor antagonists, Emend, Cinvanti and Varubi, inhibit the emetogenic effects of substance P by blocking interaction with neurokinin-1 (NK₁) receptors. NK₁ receptor antagonists have been shown to augment the antiemetic effects of dexamethasone and serotonin (5-HT₃) receptor antagonists.

Akynzeo injection for intravenous use was approved by the U.S. Food and Drug Administration (FDA) in April 2018. This intravenous formulation contains a fixed combination of a substance P/NK₁ receptor antagonist and a 5-HT₃ receptor antagonist; thus, targeting two different antiemetic pathways to prevent nausea and vomiting during both the acute and delayed phases following cancer chemotherapy.

Aloxi® (palonosetron HCl) is approved by the FDA in adults 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.

Aloxi® is FDA approved in pediatric patients aged 1 month to less than 17 years for:
- Prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

Emend® (fosaprepitant dimeglumine), in combination with other antiemetic agents, is FDA approved 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.
• Prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Anzemet® (dolasetron mesylate) has no FDA approved indications for prevention of acute and delayed nausea and vomiting associated with cancer chemotherapy.

Varubi® (rolapitant), in combination with other antiemetic agents, is FDA approved in adults for:
• Prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

**NOTE: In January 2018, the FDA and drug manufacturer issued an important drug warning for Varubi (rolapitant) injectable emulsion. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been associated with use of Varubi (rolapitant) injectable emulsion. Varubi (rolapitant) injectable emulsion has since been discontinued.

Cinvanti™ (aprepitant), in combination with other antiemetic agents, is FDA approved 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.
• Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Sustol® (granisetron), in combination with other antiemetic agents, is FDA approved 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.

Akynzeo® (fosnetupitant and palonosetron), in combination with dexamethasone, is FDA approved in adults for:
• Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

**Background**
Nausea and vomiting are common during chemotherapy. The National Comprehensive Cancer Network (NCCN) has developed a list of specific chemotherapy agents that are considered highly emetogenic with guidelines for use of antiemetic medications (see table in Policy Guidelines section).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

**Policy**

BCBSNC will provide coverage for injectable antiemetics, including selective serotonin (5-HT3) receptor antagonists, palonosetron (Aloxi®) and granisetron (Sustol®), neurokinin-1 (NK1) receptor antagonists, fosaprepitant (Emend®) and aprepitant (Cinvanti™), and combined NK1/5-HT3 receptor antagonist fosnetupitant/palonosetron (Akynzeo®), for treatment of nausea and vomiting associated with chemotherapy when the medical necessity criteria and guidelines shown below are met.

BCBSNC considers injectable/intravenous Anzemet® (dolasetron mesylate) 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.
Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Antiemetic Injection Therapy is covered

Nausea and vomiting associated with cancer chemotherapy

1. Use of Emend® (fosaprepitant) antiemetic injectable therapy may be considered medically necessary for:
   a. Adults for the prevention of acute and delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a moderately or highly emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy Guidelines); OR
   b. Patients with documented use of a low or minimally emetogenic cancer chemotherapy agent(s), and the patient has had an inadequate response with prior use of oral or intravenous granisetron or oral or intravenous ondansetron; OR has an FDA labeled contraindication to use of oral or intravenous granisetron or oral or intravenous ondansetron.

2. Use of Aloxi® (palonosetron) antiemetic injectable therapy may be considered medically necessary for:
   a. Pediatric patients aged 1 month to less than 17 years (based on FDA statement) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of a highly emetogenic cancer chemotherapy when there is documented use of a highly emetogenic chemotherapy agent(s) as listed in the most recent NCCN Guidelines (see Policy Guidelines); OR
   b. Adult patients aged 17 years and older (based on FDA statement) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of a moderately and/or highly emetogenic cancer chemotherapy; OR
   c. Patients with documented use of a low or minimally emetogenic cancer chemotherapy agent(s), and the patient has had an inadequate response with prior use of oral or intravenous granisetron or oral or intravenous ondansetron; OR has an FDA labeled contraindication to use of oral or intravenous granisetron or oral or intravenous ondansetron [applies to both adult and pediatric patients].

3. Use of Cinvanti™ (aprepitant) antiemetic injectable therapy may be considered medically necessary for:
   a. Adults for the prevention of acute and delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a moderately and/or highly emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy Guidelines); AND
   b. Patients with documented concomitant use of dexamethasone and a serotonin (5-HT3) receptor antagonist OR who have an FDA labeled contraindication or intolerance to dexamethasone or serotonin (5-HT3) receptor antagonists.

4. Use of Sustol® (granisetron) antiemetic injectable therapy may be considered medically necessary for:
   a. Adults for the prevention of acute and delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a moderately emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy
Guidelines) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimen [highly emetogenic chemotherapy (HEC)]; OR

b. Patients with documented use of a low or minimally emetogenic cancer chemotherapy agent(s), and the patient has had an inadequate response with prior use of oral or intravenous granisetron or oral or intravenous ondansetron; OR has an FDA labeled contraindication to use of oral or intravenous granisetron or oral or intravenous ondansetron.

5. Use of Akynzeo® (fosnetupitant and palonosetron) antiemetic injectable therapy may be considered medically necessary for:
   a. Adults for the prevention of acute and delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a highly and/or moderately emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy Guidelines); AND
   b. The patient has had an inadequate response with prior use of Emend OR has a contraindication to use of Emend; AND
   c. The patient has had an inadequate response with prior use of oral or intravenous granisetron or oral or intravenous ondansetron; OR has a contraindication to use of oral or intravenous granisetron or oral or intravenous ondansetron.

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:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR
- 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.

When Antiemetic Injection Therapy is not covered

Use of Aloxi® (palonosetron HCl), Sustol® (granisetron), Emend® (fosaprepitant dimeglumine), Cinvanti™ (aprepitant), and Akynzeo® (fosnetupitant/palonosetron) injectable therapy is considered not medically necessary when criteria under the “When covered” are not met.

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).

Emend® (fosaprepitant dimeglumine) is considered investigational for use in the pediatric population, defined as below 18 years of age.

Antiemetic Injection Therapy is considered investigational when used for:

1. Non-cancer indications; OR

2. When criteria are not met regarding FDA labeling OR strong endorsement/support by nationally recognized compendia, as stated under “When Antiemetic Injection Therapy is covered.”

Policy Guidelines
The U.S. Food and Drug Administration (FDA) released a safety announcement on December 17, 2010 stating that the injection form of Anzemet® (dolasetron mesylate) should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric and adult patients. New data demonstrate that Anzemet® injection can increase the risk of developing an abnormal heart rhythm (torsade de pointes), which in some cases can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Anzemet® causes a dose-dependent prolongation in the QT, PR, and QRS intervals on an electrocardiogram (ECG).

Anzemet® tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this drug is less than that seen with the injection form. However, a stronger warning about this potential risk is being added to the Warnings and Precautions sections of the Anzemet® tablet label. Anzemet® tablets may also still be used for prevention of PONV.

In January 2018, the FDA and drug manufacturer issued an important drug warning for Varubi (rolapitant) injectable emulsion. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been associated with use of Varubi (rolapitant) injectable emulsion. Varubi (rolapitant) injectable emulsion has since been discontinued.

Akynzeo for injection has not been studied for prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy regimens.

<table>
<thead>
<tr>
<th>Moderately and Highly Emetogenic Chemotherapy</th>
<th>Table based on NCCN Guidelines Version 1.2018 Antiemesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous Agents High Emetic Risk (&gt;90% frequency of emesis)</strong></td>
<td>AC combination defined as either doxorubicin or epirubicin with cyclophosphamide</td>
</tr>
<tr>
<td>Carboplatin AUC ≥4</td>
<td>Doxorubicin ≥60 mg/m²</td>
</tr>
<tr>
<td>Carmustine &gt;250 mg/m²</td>
<td>Epirubicin &gt;90 mg/m²</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Ifosfamide ≥2 g/m² per dose</td>
</tr>
<tr>
<td>Cyclophosphamide &gt;1500 mg/m²</td>
<td>Streptozocin</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td></td>
</tr>
</tbody>
</table>

| **Intravenous Agents Moderate Emetic Risk (30-90% frequency of emesis)** | Dinutuximab |
| Aldesleukin >12-15 million IU/m² | |
| Amifostine >300 mg/m² | |
| Epirubicinaa <90 mg/m² | |
| Azacitidine | |
| Idarubicin | |
| Ifosfamideaa <2 g/m² per dose | |
| Busulfan | |
| Interferon alfa ≥10 million IU/m² | |
| Carboplatform < 4 | |
| Epirubicinaa <60 mg/m² | |
| Carmustineaa ≤250 mg/m² | |
| Clofarabine | |
| Methotrexateaa ≥250 mg/m² | |
| Cyclophosphamide ≤1500 mg/m² | |
| Cytarabine >200 mg/m² | |
| Dactinomycinaa | |
| Oxaliplatinaa | |
| Temozolomide | |
| Trabectedinaa | |
Oral Agents Moderate to High Emetic Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Agents Moderate to High Emetic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin**</td>
<td>Dual-drug liposomal encapsulation of cytarabine and daunorubicin</td>
</tr>
<tr>
<td>Altretamine</td>
<td>Midostaurin</td>
</tr>
<tr>
<td>Busulfan (≥4 mg/day)</td>
<td>Mitotane</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Niraparib</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Olaparib</td>
</tr>
<tr>
<td>Cyclophosphamide (≥100 mg/m²/day)</td>
<td>Panobinostat</td>
</tr>
<tr>
<td>Enasidenib</td>
<td>Procarbazine</td>
</tr>
<tr>
<td>Estramustine</td>
<td>Rucaparib</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Temozolomide (≥75 mg/m²/day)</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Trifluridine/tipiracil</td>
</tr>
<tr>
<td>Lomustine (single day)</td>
<td></td>
</tr>
</tbody>
</table>

**These agents may be highly emetogenic in certain patients.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), “Investigational (Experimental) Services.”

Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursable. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: C9399, J0185, J1260, J1453, J1454, J1627, J2469, J2797, J3490, S0353, S0354

The following diagnostic ranges that are subject to medical necessity review:

ICD-10 Codes: C00.0-C49.9, C4A.0-C4A.9, C50.01-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

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


U.S. Food and Drug Administration (FDA). EMEND (fosaprepitant dimeglumine) injection


Medical Director review 5/2015


Medical Director review 9/2016

Specialty Matched Consultant Advisory Panel review 3/2017


Specialty Matched Consultant Advisory Panel review 3/2018


Policy Implementation/Update Information

7/1/15  Policy titled, “Antiemetic Injection Therapy” created. Policy Statement as follows, “BCBSNC will provide coverage for injectable antiemetics, including selective serotonin (5-HT3) receptor antagonists, palonosetron (Aloxi®), and neurokinin-1 (NK1) receptor antagonist, fosaprepitant (Emend®), for treatment of nausea and vomiting associated with chemotherapy when the medical necessity criteria and guidelines shown below are met. BCBSNC considers injectable/intravenous Anzemet® (dolasetron mesylate) investigational for the prevention and/or treatment of acute and delayed nausea and vomiting related to use of any cancer chemotherapy agent(s)”.

Medical Director review 5/2015. Policy notified 7/1/2015 for effective date 10/1/15. (td)

7/28/15  “When Covered” section updated to change 17 years to 18 years in number 2. a. Billing/Coding section updated to include: The following diagnostic ranges that are subject to medical necessity review: ICD-9 Codes: 140.0-209.36, 209.70-209.79, 230.0-234.9 and ICD-10 Codes: 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 (td)

9/1/15  When Covered section updated for clarity. References updated. (td)


4/29/16  Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

12/30/16  Added ICD-10 codes Z51.11, Z51.12 and HCPCS codes S0353, S0354 to the Billing/Coding section. No change to policy statement. Notification given 12/30/16 for effective date 4/1/17. (lpr)

4/28/17  Added the following statement to “When Covered” section: “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: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR 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”. Under “When Not Covered” section, added the statement “Antiemetic Injection Therapy is considered investigational when used for: 1) Non-cancer indications; OR 2) When criteria are not met regarding FDA labeling OR
strong endorsement/ support by nationally recognized compendia, as stated under “When Antiemetic Injection Therapy is covered.” Added the following statements under “Policy Guidelines” section: 1) Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services.” 2) Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia. Medical director review 3/2017. Specialty Matched Consultant Advisory Panel review 3/29/2017. Updated NCCN antiemesis table. Reference added. No change to policy statement. (lpr)

9/15/17 Added ICD-10 codes D47.01, D47.02, D47.09 to Billing/Coding section for effective date 10/1/17. (lpr)

3/29/18 Updated “Description of Procedure or Service” section to include indications for three additional antiemetic drugs: Varubi (rolapitant), Cinvanti (aprepitant), and Sustol (granisetron). Added the following statements to “When Covered” section: “3) Use of Varubi® (rolapitant) antiemetic injectable therapy may be considered medically necessary for: a. Adults for the prevention of delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a moderately and/or highly emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy Guidelines); AND b. Patients with documented concomitant use of dexamethasone and a serotonin (5-HT3) receptor antagonist OR who have an FDA labeled contraindication or intolerance to dexamethasone or serotonin (5-HT3) receptor antagonists. 4) Use of Cinvanti™ (aprepitant) antiemetic injectable therapy may be considered medically necessary for: a. Adults for the prevention of acute and delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a moderately and/or highly emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy Guidelines); AND b. Patients with documented concomitant use of dexamethasone and a serotonin (5-HT3) receptor antagonist OR who have an FDA labeled contraindication or intolerance to dexamethasone or serotonin (5-HT3) receptor antagonists. 5) Use of Sustol® (granisetron) antiemetic injectable therapy may be considered medically necessary for: a. Adults for the prevention of acute and delayed nausea and vomiting related to cancer chemotherapy when there is documented use of a moderately emetogenic chemotherapy agent(s) listed in the most recent NCCN Guidelines (see Policy Guidelines) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimen; OR b. Patients with documented use of a low or minimally emetogenic cancer chemotherapy agent(s), and the patient has had an inadequate response with prior use of oral or intravenous granisetron or oral or intravenous ondansetron; OR has an FDA labeled contraindication to use of oral or intravenous granisetron or oral or intravenous ondansetron”. Under “When Not Covered” section, added three additional antiemetic drugs: Varubi (rolapitant), Cinvanti (aprepitant), and Sustol (granisetron). Added HCPCS codes C9399, J1627, J3490 in Billing/Coding section. Specialty Matched Consultant Advisory Panel review 3/2018. Updated NCCN antiemesis table. References added. Notification given 3/29/18 for effective date 6/29/18. (krc)

5/25/18 Codes C9463 and C9464 added to Billing/Coding section effective 4/1/18. Policy remains on notice until 6/29/18. (krc)

7/13/18 Updated policy to include information and criteria for Akynzeo (fosnetupitant/palonosetron). “When Covered” section revised to include medically necessary criteria for Akynzeo under item #6. Description and Policy Guidelines sections updated to reflect addition of Akynzeo. References added. (krc)

8/10/18 Updated “When Covered” section to provide the following clarification for Sustol: “or anthracycline and cyclophosphamide (AC) combination chemotherapy regimen [highly emetogenic chemotherapy (HEC)].” Reference added. Medical Director review 7/2018. (krc)

9/28/18 Code C9033 added to Billing/Coding section effective 10/1/18. (krc)
12/31/18  Added HCPCS codes J0185, J1454, and J2797 to Billing/Coding section and deleted codes C9033, C9463, and C9464 effective 1/1/19. (krc)

4/16/19  Specialty Matched Consultant Advisory Panel review 3/20/2019. No change to policy statement. (krc)

5/26/20  Removed policy statements for Varubi (rolapitant) injectable emulsion, as product has been discontinued. Added the following statement to Description and Policy Guidelines sections: “In January 2018, the FDA and drug manufacturer issued an important drug warning for Varubi (rolapitant) injectable emulsion. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been associated with use of Varubi (rolapitant) injectable emulsion. Varubi (rolapitant) injectable emulsion has since been discontinued.” Reference added. Specialty Matched Consultant Advisory Panel review 3/18/2020. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.