Clinical Policy: Netupitant and Palonosetron (Akynzeo), Fosnetupitant and Palonosetron (Akynzeo IV)

Reference Number: CP.PMN.158
Effective Date: 09.01.06
Last Review Date: 08.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Netupitant/palonosetron (Akynzeo®) and fosnetupitant/palonosetron are fixed combination products of netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron hydrochloride, a serotonin ($5\text{-}HT_3$) receptor antagonist.

FDA Approved Indication(s)

Akynzeo capsules are 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 for injection and Akynzeo injection are 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.

- Limitation(s) of use: Akynzeo for injection and Akynzeo injection have not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Akynzeo is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Prevention of Nausea and Vomiting Associated with Cancer Chemotherapy (must meet all)**:**

1. Prescribed for the prevention of chemotherapy-induced nausea/vomiting;
2. Age ≥ 18 years;
3. Member is scheduled to receive moderately to highly emetogenic cancer chemotherapy (*see Appendix D*);
4. Member meets one of the following (a or b):*
   **For Illinois HIM requests, the step therapy requirements below do not apply for formulary agents as of 1/1/2026 per IL HB 5395.*
   a. Both of the following (i and ii):

i. Failure of a 5-HT_3 receptor antagonist (*ondansetron is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
ii. Failure of an NK_1 antagonist (*aprepitant is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization is required for aprepitant*

b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;

5. Prescribed in combination with dexamethasone;
6. Dose does not exceed one of the following (a or b):
   a. Akynzeo capsules: netupitant 300 mg/palonosetron 0.5 mg (1 capsule) per chemotherapy cycle;
   b. Akynzeo for injection/Akynzeo injection: fosnetupitant 235 mg/palonosetron 0.25 mg (1 vial) per chemotherapy cycle.

Approval duration: Projected course of chemotherapy

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Prevention of Nausea and Vomiting Associated with Cancer Chemotherapy (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Prescribed in combination with dexamethasone;

4. Member continues to receive moderately to highly emetogenic cancer chemotherapy (*see Appendix D*);
5. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Akynzeo capsules: netupitant 300 mg/palonosetron 0.5 mg (1 capsule) per chemotherapy cycle;
   b. Akynzeo for injection/Akynzeo injection: fosnetupitant 235 mg/palonosetron 0.25 mg (1 vial) per chemotherapy cycle.

Approval duration: Projected course of chemotherapy

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

$5HT_3$: serotonin 5-hydroxytryptamine, type 3
ASCO: American Society of Clinical Oncology
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
NK_1: neurokinin 1

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
5-HT$_3$ Serotonin Antagonists		
Aloxi® (palonosetron)	0.25 mg IV given 30 min prior to chemotherapy	0.25 mg/day
Anzemet® (dolasetron)	100 mg PO within 1 hr prior to chemotherapy	100 mg/day
granisetron (Kytril®)	Tablet: 2 mg PO QD given 1 hr prior to chemotherapy, or 1 mg PO BID (one dose given 1 hr prior to chemotherapy and then 12 hours later) Injection: 10 mcg/kg IV given within 30 min prior to chemotherapy (on days chemotherapy is given)	PO: 2 mg/day PO IV: 10 mcg/kg/day
ondansetron (Zofran®, Zofran® ODT, Zuplenz®)	**Prevention of nausea and vomiting associated with moderately emetogenic chemotherapy** Age 12 years or older: 8 mg PO given 30 min prior to chemotherapy, then repeat dose 8 hrs after initial dose, then 8 mg PO BID for 1 to 2 days after chemotherapy completion Age 4 to 11 years: 4 mg PO given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose, then 8 mg PO TID for 1 to 2 days after chemotherapy completion **Prevention of nausea and vomiting associated with highly emetogenic chemotherapy** 24 mg PO given 30 min prior to start of single-day chemotherapy	PO: 24 mg/day IV: 16 mg/dose (up to 3 doses/day)
NK$_1$ Antagonists		
aprepitant (Emend®)	*Capsules:* 125 mg PO on day 1 and 80 mg PO on days 2 and 3 *Oral suspension*: 3 mg/kg PO on Day 1, then 2 mg/kg PO on Days 2 and 3	Day 1: 125 mg Days 2 and 3: 80 mg
Emend® (fosaprepitant)	150 mg IV on day 1 (for single dose chemo regimens)	Day 1: 150 mg
Cinvanti® (aprepitant)	*HEC or MEC (single-dose regimen):* 130 mg IV on Day 1 *MEC (3-day regimen):* 100 mg IV on Day 1	Single-dose: 130 mg/dose 3-day regimen: 100 mg/dose

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Varubi™ (rolapitant)	180 mg as a single dose 2 hours prior to the initiation of each chemotherapy, but at no less than 2 week intervals. *Administer in combination with dexamethasone and a 5-HT_3 receptor antagonist*	180 mg

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Recommendations in Oncology

- Minimal emetic risk chemotherapy: No routine prophylaxis is recommended.
- Low emetic risk chemotherapy: Recommended options include dexamethasone (recommended by both ASCO and NCCN) or metoclopramide, prochlorperazine, or a 5-HT_3 receptor antagonist (recommended by NCCN only). NK_1 receptor antagonists are not included in low risk antiemetic recommendations.
- Moderate emetic risk chemotherapy: 5-HT_3 receptor antagonists and dexamethasone may be used in combination and with or without NK_1 receptor antagonists. Olanzapine may also be used in combination with palonosetron and dexamethasone.
  - Examples of moderate emetic risk chemotherapy: bendamustine, carboplatin AUC < 4, carmustine ≤ 250 mg/m^2, clofarabine, cyclophosphamide ≤ 1,500 mg/m^2, cytarabine > 200 mg/m^2, daunorubicin, doxorubicin < 60 mg/m^2, epirubicin ≤ 90 mg/m^2, idarubicin, ifosfamide < 2 g/m^2 per dose, irinotecan, methotrexate ≥ 250 mg/m^2, oxaliplatin
- High emetic risk chemotherapy: NK_1 receptor antagonists are recommended for use in combination with 5-HT_3 receptor antagonists and dexamethasone. Olanzapine may also be used in combination with 5-HT_3 receptor antagonists, dexamethasone, and/or NK_1 receptor antagonists.
  - Examples of high emetic risk chemotherapy: carboplatin AUC ≥ 4, carmustine > 250 mg/m^2, cisplatin, cyclophosphamide > 1,500 mg/m^2, dacarbazine, doxorubicin ≥ 60 mg/m^2, epirubicin > 90 mg/m^2, fam-trastuzumab deruxtecan-nxki, ifosfamide ≥ 2 mg/m^2 per dose, mechlorethamine, sacituzumab govitecan-hziy, streptozocin
- Breakthrough emesis: Per NCCN, an agent from a different drug class is recommended to be added to the current antiemetic regimen. Drug classes include atypical antipsychotics (olanzapine), benzodiazepines (lorazepam), cannabinoids (dronabinol, nabilone), phenothiazines (prochlorperazine, promethazine), 5-HT_3 receptor antagonists (dolasetron, ondansetron, granisetron), corticosteroids (dexamethasone), or haloperidol, metoclopramide, scopolamine. An NK_1 receptor antagonist may be added to the prophylaxis regimen of the next chemotherapy cycle if not previously included.

Appendix E: States with Regulations against Redirections in Certain Oncology Settings

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes[≠]	For stage 4 advanced, metastatic cancer or associated conditions. [≠]Exception if clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
MS	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial and HIM requests only** For stage 4 metastatic cancer and associated conditions
OK	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes[^]	For stage 4 advanced metastatic cancer, metastatic blood cancer, and associated conditions [^]Exception if step therapy is for AB-rated generic equivalent, interchangeable biological product, or biosimilar product to the equivalent brand drug
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Prevention of chemotherapy-induced nausea and vomiting	1 capsule PO given 1 hr prior to chemotherapy on Day 1, in combination with dexamethasone or 1 vial infused IV over 30 minutes starting 30 minutes before chemotherapy on Day 1, in combination with dexamethasone	1 capsule or 1 vial on Day 1 of chemotherapy cycle

VI. Product Availability

- Capsule: 300 mg netupitant/0.5 mg palonosetron
- Single dose vial, powder for reconstitution: 235 mg fosnetupitant/0.25 mg palonosetron
- Single dose vial, injection solution: 235 mg fosnetupitant/0.25 mg palonosetron per 20 mL
  - Ready-to-use (with hanger)
  - To-be-diluted

VII. References

1. Akynzeo Prescribing Information. Dublin, Ireland: Helsinn Healthcare; February 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/210493Orig1s005lbl.pdf. Accessed April 18, 2025.
2. Hesketh, PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Guideline Update. *J Clin Oncol*. 2020. 38(24):2782-2797.
3. National Comprehensive Cancer Network. Antiemesis Version 1.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed May 12, 2025.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1454	Injection, fosnetupitant 235 mg and palonosetron 0.25 mg
J8655	Netupitant 300 mg and palonosetron 0.5 mg, oral

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; added coding implications; references reviewed and updated.	11.13.20	02.21
Added allowance for bypassing redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings with additional details in appendix E.	04.27.21	
Added Nevada to Appendix E.	08.03.21	
1Q 2022 annual review: removed distinction between oral and IV versions for moderate vs high emetogenic risk per NCCN 1.2021 antiemesis guidelines; references reviewed and updated.	10.04.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.04.22	
1Q 2023 annual review: added requirement that member is scheduled to receive moderately to highly emetogenic cancer chemotherapy to align with other clinical policies for drugs used for this indication; modified to generalize beyond Stage IV or metastatic cancer to the following redirection bypass: "Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings"; references reviewed and updated.	10.10.22	02.23
RT4: for Akynzeo IV, added ready-to-use injection solution formulation.	03.02.23	
Added Commercial line of business per HP request.	03.03.23	05.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2023 annual review: added requirement for continuation of therapy that member continues to receive moderately to highly emetogenic cancer chemotherapy; references reviewed and updated; updated Appendix E to include Oklahoma.	04.17.23	08.23
Updated Appendix E to include Mississippi.	06.05.24	
3Q 2024 annual review: no significant changes; references reviewed and updated.	05.09.24	08.24
3Q 2025 annual review: no significant changes; added step therapy bypass for IL HIM per IL HB 5395; updated Appendix E with revised language and exception for Tennessee; references reviewed and updated.	04.18.25	08.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise

professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.