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

Reference Number: CP.PMN.158
Effective Date: 09.01.06
Last Review Date: 02.21
Line of Business: 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 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.

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. If request is for Akynzeo capsules, member is scheduled to receive moderately to highly emetogenic cancer chemotherapy (*see Appendix D*);
4. If request is for Akynzeo for injection, member is scheduled to receive highly emetogenic cancer chemotherapy (*see Appendix D*);
5. Failure of a $5\text{-}HT_3$ receptor antagonist (*ondansetron is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. 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*

7. Prescribed in combination with dexamethasone;
8. 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: fosnetupitant 235 mg/palonosetron 0.25 mg (1 vial) per chemotherapy cycle.

Approval duration: Projected course of chemotherapy

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): 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. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for Akynzeo capsules, member continues to receive moderately to highly emetogenic cancer chemotherapy; (*see Appendix D*);
4. If request is for Akynzeo for injection, member continues to receive highly emetogenic cancer chemotherapy (*see Appendix D*);
5. Prescribed in combination with dexamethasone;
6. 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: 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. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): 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 –

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)	**Prevention of nausea and vomiting associated with chemotherapy** 0.25 mg IV given 30 min prior to chemotherapy	0.25 mg/day
Anzemet® (dolasetron)	**Prevention of nausea and vomiting associated with chemotherapy** 100 mg PO within 1 hr prior to chemotherapy	100 mg/day
granisetron (Kytril®)	**Prevention of nausea and vomiting associated with chemotherapy** 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	PO: 24 mg/day IV: 16 mg/dose (up to 3 doses/day)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Prevention of nausea and vomiting associated with highly emetogenic chemotherapy 24 mg PO given 30 min prior to start of single-day chemotherapy **Prevention of nausea and vomiting associated with emetogenic chemotherapy** 0.15 mg/kg/dose IV given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose	
Sancuso® (granisetron)	**Prevention of nausea and vomiting associated with chemotherapy** Apply 1 patch at least 24 hrs prior to chemotherapy; may be applied up to 48 hrs after chemotherapy	1 patch/7 days
Sustol® (granisetron)	**Prevention of moderately emetogenic chemotherapy or anthracycline/cyclophosphamide chemotherapy** 10 mg SC given 30 min prior to chemotherapy on day 1 (in combination with other agents). Do not administer more frequently than once every 7 days.	10 mg/7 days
NK_1 Antagonists		
aprepitant (Emend®)	**Prevention of nausea and vomiting associated with moderately to highly emetogenic chemotherapy** *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)	**Prevention of nausea and vomiting associated with moderately to highly emetogenic chemotherapy** 150 mg IV on day 1 (for single dose chemo regimens)	Day 1: 150 mg
Varubi™ (rolapitant)	**Prevention of nausea and vomiting associated with moderately to highly emetogenic chemotherapy** 180 mg PO on day 1	Day 1: 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: azacitidine, alemtuzumab, bendamustine, carboplatin, clofarabine, cyclophosphamide < 1,500 mg/m^2, cytarabine < 1,000 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, 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: carmustine, cisplatin, cyclophosphamide ≥ 1,500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, 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), steroids (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.

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

VII. References

1. Akynzeo Prescribing Information. Woodcliff Lake, NJ: Eisai, Inc.; June 2020. Available at: https://www.akynzeo.com/. Accessed November 13, 2020.
2. Hesketh, PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017: JCO2017744789.
3. National Comprehensive Cancer Network. Antiemesis Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed November 13, 2020.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com/.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 13, 2020.

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
Policy created.	01.17	
3Q 2018 annual review: policies combined for HIM and Medicaid lines of business; For Medicaid, policy split from CP.PMN.11 Oral Antiemetics into individual policies; For HIM and Medicaid: added requirement that member is scheduled to receive moderately to highly emetogenic cancer chemo per NCCN recommendations; modified trial and failure of ondansetron and granisetron to require one 5-HT_3 receptor antagonist (ondansetron is preferred for both lines of business); added trial and failure of an NK_1 antagonist (aprepitant is preferred); added requirement that Akynzeo must be prescribed in combination with dexamethasone per FDA labeling for initial and continued approval; specified that member must be receiving moderately to highly emetogenic chemotherapy for initial and continued approval; revised max dose requirement to per chemotherapy cycle; For HIM: added age requirement,; For Medicaid: removed requirement that 5-HT_3 receptor antagonist must be tried in the last 60 days, modified approval duration for chemotherapy-induced N/V to duration of chemotherapy; references reviewed and updated.	05.15.18	08.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.30.18	02.19
RT4: Akynzeo IV formulation added.	06.21.19	
1Q 2020 annual review: no significant changes; revised HIM-Medical Benefit to HIM; references reviewed and updated.	01.22.20	02.20
New IV dosage formulation added.	07.20.20	
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

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.