RxAdvance

Clinical Policy Title:	netupitant/palonosetron, fosnetupitant/palonosetron
Policy Number:	RxA.334
Drug(s) Applied:	Akynzeo®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

- 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 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.
- Akynzeo® is a combination of palonosetron, a serotonin-3 (5-HT_3) receptor antagonist, and netupitant or fosnetupitant, substance P/neurokinin-1 (NK-1) receptor antagonists: palonosetron prevents nausea and vomiting during the acute phase and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

Limitations 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.

Dosing Information

Drug Name	Indication	Dosing Regimen*	Maximum Dose
fosnetupitant/ palonosetron (Akynzeo® IV)	Prevention of chemotherapy- induced nausea and vomiting	fosnetupitant 235 mg; palonosetron 0.25 mg) infused intravenous over 30 minutes starting 30 minutes before chemotherapy on Day 1, in combination with dexamethasone.	235 mg fosnetupitant/0.25 mg palonosetron infused intravenously.
netupitant/ palonosetron (Akynzeo® capsules)	Prevention of chemotherapy- induced nausea and vomiting	netupitant 300 mg; palonosetron 0.5 mg) orally as a single dose approximately 60 minutes prior to chemotherapy in combination with dexamethasone.	300 mg netupitant/0.5 mg palonosetron) orally as a single dose

*Hepatic Impairment: Avoid use in patients with severe hepatic impairment.
Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease.

Dosage Forms

- Capsules: 300 mg netupitant/0.5 mg palonosetron
- Single dose vial: powder for reconstitution and solution for injection: 235 mg fosnetupitant/0.25 mg palonosetron

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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® IV, member is scheduled to receive highly emetogenic cancer chemotherapy (see Appendix D);
5. Failure of a 5-HT3 receptor antagonist (ondansetron is preferred) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Failure of an NK1 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. If request is for Akynzeo® capsules, Dose does not exceed netupitant 300 mg/palonosetron 0.5 mg (1 capsule) per chemotherapy cycle;
9. If request is for Akynzeo® for injection, dose does not exceed fosnetupitant 235 mg/palonosetron 0.25 mg (1 vial) per chemotherapy cycle.

Approval Duration

Commercial: Projected course of chemotherapy

Medicaid: Projected course of chemotherapy

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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 of Akynzeo® capsules, new dose does not exceed netupitant 300 mg/palonosetron 0.5 mg (1 capsule) per chemotherapy cycle;
7. If request is for a dose increase of Akynzeo® for injection, new dose does not exceed fosnetupitant 235 mg/palonosetron 0.25 mg (1 vial) per chemotherapy cycle.

Approval Duration

Commercial: Projected course of chemotherapy

Medicaid: Projected course of chemotherapy

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

5HT3: serotonin 5-hydroxytryptamine, type 3
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
NK1: neurokinin 1
ASCO: American Society of Clinical Oncology

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
*5-HT3 Serotonin A*ntagonists		
palonosetron (Aloxi®)	**Prevention of nausea and vomiting associated with chemotherapy** 0.25 mg intravenous given 30 min prior to chemotherapy	0.25 mg Intravenously/day
dolasetron (Anzemet®)	**Prevention of nausea and vomiting associated with chemotherapy** 100 mg Orally /within 1 hour prior to chemotherapy	100 mg/day
ondansetron (Zofran®, Zofran® ODT, Zuplenz®)	**Prevention of nausea and vomiting associated with moderately emetogenic chemotherapy** Age 12 years or older: 8 mg orally given 30 min prior to chemotherapy, then repeat dose 8 hrs after initial dose, then 8 mg orally twice daily for 1 to 2 days after chemotherapy completion Age 4 to 11 years: 4 mg orally given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose, then 8 mg orally three times daily for 1 to 2 days after chemotherapy completion **Prevention of nausea and vomiting associated with highly emetogenic chemotherapy** 24 mg orally given 30 min prior to start of single-day chemotherapy **Prevention of nausea and vomiting associated with emetogenic chemotherapy** 0.15 mg/kg/dose intravenous given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose	orally: 24 mg/day Intravenous: 16 mg/dose (up to 3 doses/day)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
5-HT3 Serotonin Antagonists		
granisetron (Kytril®)	**Prevention of nausea and vomiting associated with chemotherapy** Tablet: 2 mg orally once daily given 1 hr prior to chemotherapy, or 1 mg orally twice daily (one dose given 1 hr prior to chemotherapy and then 12 hours later) Injection: 10 mcg/kg intravenous given within 30 min prior to chemotherapy (on days chemotherapy is given)	orally: 2 mg/day orally intravenous: 10 mcg/kg/day
granisetron (Sancuso®)	**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
granisetron (Sustol®)	**Prevention of moderately emetogenic chemotherapy or anthracycline/cyclophosphamide chemotherapy** 10 mg subcutaneous 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
NK1 Antagonists		
aprepitant (Emend®)	**Prevention of nausea and vomiting associated with moderately to highly emetogenic chemotherapy** Capsules: 125 mg orally on day 1 and 80 mg orally on days 2 and 3. Oral suspension: 125 mg orally 1 hour before chemotherapy. on Day 1, then 80 mg orally 1 hour before chemotherapy on Days 2 and 3.	Day 1: 125 mg Days 2 and 3: 80 mg
fosaprepitant (Emend®)	**Prevention of nausea and vomiting associated with moderately to highly emetogenic chemotherapy** 150 mg intravenous on day 1 (for single dose chemo regimens)	Day 1: 150 mg
(Varubi™)	**Prevention of nausea and vomiting associated with moderately to highly emetogenic chemotherapy** 180 mg orally on day 1	Day 1: 180 mg

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

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

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- HT3 receptor antagonist (recommended by NCCN only). NK1 receptor antagonists are not included in low-risk antiemetic recommendations.
- Moderate emetic risk chemotherapy: 5-HT3 receptor antagonists and dexamethasone may be used in combination and with or without NK1 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: NK1 receptor antagonists are recommended for use in combination with 5-HT3 receptor antagonists and dexamethasone. Olanzapine may also be used in combination with 5-HT3 receptor antagonists, dexamethasone, and/or NK1 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-HT3 receptor antagonists (dolasetron, ondansetron, granisetron), steroids (dexamethasone), or (haloperidol, metoclopramide, scopolamine). An NK1 receptor antagonist may be added to the prophylaxis regimen of the next chemotherapy cycle if not previously included.

References

1. Akynzeo® Prescribing Information. Woodcliff Lake, NJ: Eisai, Inc.; April 2018. Available at: https://www.akynzeo.com/. Accessed August 16, 2021.
2. Hesketh, PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017: JCO2017744789. Available at: https://pubmed.ncbi.nlm.nih.gov/28759346/. Accessed August 16, 2021.
3. National Comprehensive Cancer Network. Antiemesis Version 1.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf . Accessed August 16, 2021.
4. Clinical Pharmacology [database online].Elsevier Inc. RELX Group™ . Available at: http://www.clinicalpharmacology-ip.com/. Accessed August 16, 2021.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed August 16, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Background was rephrased to "Akynzeo® is a combination of palonosetron .." for better explanation. 2. Background was updated to include Limitations of Use "Akynzeo® for injection and Akynzeo®..". 3. Dosing information was updated to include netupitant/ palonosetron, in order to separate capsule dosage form from injections, for better precision. 4. Dosing information was updated to include hepatic and renal impairment parameters. 5. Dosage form was updated from “powder for reconstitution” to “powder for reconstitution and solution for injection". 6. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 7. Continued Therapy Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 8. Appendix B Dosing regimen was updated for drug "Emend" to "125 mg orally 1 hour before chemotherapy...". 9. Appendix B was updated to remove generic “rolapitant” as it is not available in market. 10. References were reviewed and updated.	08/16/2021	09/14/2021