Drug Monograph

Drug/Drug Class: **Akynzeo™ (netupitant and palonosetron) capsule/ Antiemetics**

Prepared for: MO HealthNet
Prepared by: Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.

Dosage Forms & Manufacturer:

Akynzeo™ is available as a 300 mg/0.5 mg capsule containing 300 mg of netupitant and 0.5 mg of palonosetron respectively.

Eisai Inc, Woodcliff Lake, NJ

Summary of Findings:

The efficacy of Akynzeo™ for the prevention of acute and delayed nausea and vomiting due to chemotherapy was demonstrated in two phase 3 clinical trials. Complete response rates (ie, no emesis and no rescue medication) for acute, delayed, and overall nausea and vomiting following a single cycle of moderately emetogenic chemotherapy (n=1455) were 88.4%, 76.9%, and 74.3% for Akynzeo™ plus dexamethasone compared with 85%, 69.5%, and 66.6% for palonosetron plus dexamethasone. In a second phase 3 study where patients were randomized to receive Akynzeo™ or aprepitant plus palonosetron (with all patients receiving dexamethasone) for repeated cycles of highly or moderately emetogenic chemotherapy (n=412), complete response rates for the overall phase of nausea and vomiting ranged from 81% to 92% for the Akynzeo™ arm and 76% to 88% for the aprepitant/palonosetron arm through 6 cycles of chemotherapy.

Status Recommendation:

☐ Prior Authorization (PA) Required ☐ Open Access
☐ Clinical Edit ☒ PDL

Type of PA Criteria:

☐ Increased Risk of ADE ☐ Preferred Agent
☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[4]

Chemotherapy is the most common treatment-related cause of nausea and vomiting. The incidence and severity of acute emesis in persons receiving chemotherapy varies according to many factors, including the particular drug, dose, schedule of administration, route, and individual patient variables. In most cancer patients, these symptoms can be prevented or controlled.

Dosage Form(s) [1]

Akynzeo™ is available as a 300 mg/0.5 mg capsule containing 300 mg of netupitant and 0.5 mg of palonosetron respectively.

Manufacturer [1]

Eisai Inc, Woodcliff Lake, NJ

Indication(s) [1]

Akynzeo™ is indicated to prevent acute and delayed chemotherapy-associated nausea and vomiting with initial or repeat chemotherapy courses, including highly emetogenic regimens.

Clinical Efficacy [1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Netupitant, a substance P/NK1 receptor antagonist, and palonosetron, a selective 5-HT3 receptor antagonist, are both antinausea and antiemetic drugs. Both agents are selective for the receptors. The combination product prevents acute emesis, which is caused by selective stimulation of 5-HT3 receptors, and delayed emesis, which is primarily associated with substance P-mediated activation of tachykinin family NK1 receptors.

Pharmacokinetics

	Netupitant	**Palonosetron**
Protein Binding	> 99.5%	62%
Volume of distribution	1982 L	8.3 L/kg
Metabolism	Liver, via CYP3A4 (major), CYP2C9, and CYP2D6	Liver, partial via CYP2D6, CYP3A4, and CYP1A2
Excretion	Feces, 70.7% Urine, 3.95%	Feces, 5% to 8% Urine, 85% to 93%
Half-life	80 hours	48 hours

Akynzeo™ prevented more cases of delayed nausea and vomiting than palonosetron when given to adults undergoing moderately emetogenic chemotherapy.

STUDY DESIGN	Randomized, double-blind, multicenter, phase 3 clinical trial (n=1455).
INCLUSION CRITERIA	Adults receiving the first course of moderately emetogenic chemotherapy (anthracycline plus cyclophosphamide (AC) given on Day 1) for treatment of a solid tumor.
EXCLUSION CRITERIA	Patients receiving radiation therapy.
TREATMENT REGIMEN	Patients were randomized to receive Akynzeo™ 0.5 mg at 60 minutes prior to chemotherapy plus dexamethasone 12 mg at 30 minutes prior to chemotherapy (n=724), or palonosetron 0.5 mg at 60 minutes prior to chemotherapy plus dexamethasone 20 mg at 30 minutes prior to chemotherapy (n=725) on Day 1.
RESULTS	The complete response rate (ie, no emesis and no rescue medication) for the delayed (25 to 120 hours) phase following chemotherapy on cycle 1 (primary endpoint) was significantly better in the Akynzeo™ group (76.9%) compared with the palonosetron (69.5%) group. Complete response rates for the Akynzeo™ group compared with the palonosetron group were 88.4% vs 85%, respectively, for the acute (0 to 24 hours) phase and 74.3% vs 66.6% for the overall (0 to 120 hours) phase.
SAFETY	Adverse events were similar between groups.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Severe hepatic impairment; avoid use.
- Hypersensitivity reactions, including anaphylaxis, have been reported; may occur regardless of known hypersensitivity to 5-hydroxytryptamine (5-HT3) receptor antagonists.
- Severe renal impairment or end-stage renal disease; avoid use.
- Serotonin syndrome, including fatal cases, may occur, especially with concurrent use of other serotonergic drugs (eg, SSRIs, serotonin and norepinephrine reuptake inhibitors, MAOIs, mirtazapine, fentanyl, lithium, tramadol, and IV methylene blue); monitoring recommended; discontinue use if symptoms occur.
- Avoid use with strong CYP3A4 inducers such as rifampin.

Adverse Effects [1]

Most common, ≥ 3%	Akynzeo™ (n=725)	Palonosetron (n=725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

Drug Interactions [1]

- CYP3A4 substrates: dexamethasone, midazolam, alprazolam, docetaxel, paclitaxel, cyclophosphamide, irinotecan
- CYP3A4 inducers: rifampin
- Serotonergic drugs: SSRIs, serotonin norepinephrine reuptake inhibitors

Dosage and Administration [1]

The recommended dose is netupitant 300 mg/palonosetron 0.5 mg orally 1 hour prior to the start of chemotherapy on Day 1 with appropriate dexamethasone dosing.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ DOSE
Netupitant/ Palonosetron	Akynzeo	Eisai	300 mg/0.5 mg capsules	1 capsule, single dose, Day 1	$518.42
Palonosetron injection	Aloxi	Eisai	0.25 mg/5 ml, single-use vial	0.25 mg, single dose, Day 1	$275.46
Aprepitant	Emend	Merck	80 mg, 125 mg capsules, combo pack	1 capsule daily, Days 1 to 3	$508.26

***Wholesale Acquisition Price**

Conclusion

Akynzeo™ is indicated to prevent acute and delayed chemotherapy-associated nausea and vomiting with initial and repeat chemotherapy courses. Palonosetron is a 5HT3 antagonist that prevents acute (0 to 24 hours) nausea and vomiting while netupitant is an NK1 antagonist that prevents nausea and vomiting during both the acute and delayed (25 to 120 hours) phases following chemotherapy. Palonosetron was previously approved as an individual oral agent, but was not marketed. The efficacy of Akynzeo™ was demonstrated in two phase 3 clinical trials.

Complete response rates (ie, no emesis and no rescue medication) for acute, delayed, and overall nausea and vomiting following a single cycle of moderately emetogenic chemotherapy (n=1455) were 88.4%, 76.9%, and 74.3% for Akynzeo™ plus dexamethasone compared with 85%, 69.5%, and 66.6% for palonosetron plus dexamethasone. In a second phase 3 study in which patients were randomized to receive Akynzeo™ or aprepitant plus palonosetron (with all patients receiving dexamethasone) for repeated cycles of highly or moderately emetogenic chemotherapy (n=412), complete response rates for the overall phase of nausea and vomiting ranged from 81% to 92% for the Akynzeo™ arm and 76% to 88% for the aprepitant/palonosetron arm through 6 cycles of chemotherapy. Akynzeo™ is well-tolerated.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List

References

1. Product Information: Akynzeo™, netupitant/palonosetron capsules. Eisai Inc, Woodcliff Lake, NJ, 10/2014
2. Aapro M, Rugo H, Rossi G et al: A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol 2014; 25(7):1328-1333.
3. Gralla RJ, Bosnjak SM, Hontsa A et al: A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 2014; 25(7):1333-1339.
4. Nausea and Vomiting (PDQ). Retrieved March 4, 2015 from http://www.cancer.gov

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