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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/22/15**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	ARCHIVE DATE:

AKYNZEO® (netupitant and palonosetron) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

AKYNZEO® (netupitant and palonosetron) oral capsule (cont.)

Description:

Akynzeo (300 mg netupitant/0.5 mg palonosetron) is indicated 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. It is an oral fixed combination product of netupitant, a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5HT3) receptor antagonist. The fixed combination acts on two pathways associated with cancer chemotherapy-induced nausea and vomiting (CINV). Netupitant and palonosetron hydrochloride are anti-nausea and anti-emetic agents.

Chemotherapy induced nausea and vomiting (CINV)

- The objective of antiemetic therapy is the complete prevention of CINV
- Cancer chemotherapy may be associated with a high incidence of nausea & vomiting, particularly when certain agents with a high emetogenic potential are used
- A limitation of current recommendations for prevention and treatment of CINV is the lack of guidance for patients receiving **oral** chemotherapy agents, which vary in their emetogenicity potential
    - Virtually all of the clinical trials evaluating prevention and treatment of CINV have focused on **intravenous** chemotherapy
    - Therefore, evidenced-based guidelines for antiemetic prophylaxis with oral chemotherapy agents are not currently possible
- There are 3 distinct types of CINV, with important implications for both prevention and management
    - Acute emesis, which most commonly begins within 1-2 hours of chemotherapy & usually peaks in 4-6 hours
        - The development of acute emesis is known to depend on serotonin (5-HT3) & stimulation its receptors have been demonstrated to selectively stimulate the emetic response
    - Delayed emesis, occurring more than 24 hours after chemotherapy, peaks in 2-3 days & may persist for 5 days
        - Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK1) receptors by substance P
            - NK1 receptors are broadly distributed in the central and peripheral nervous systems
    - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant nausea & vomiting during previous cycles of chemotherapy
    - Other categories of emesis are described & include:
        - Anticipatory emesis
            - Occurs before chemotherapy, in patients who experienced nausea & vomiting from previous chemotherapy
            - Conditioned responses in those who experience severe nausea & vomiting during prior cycles of chemotherapy be induced by sensory cues and cognitive anticipation of subsequent chemotherapy
            - Behavioral therapy or benzodiazepines are effective
        - Breakthrough emesis
            - Occurs within 5 days of chemotherapy & after use of prophylactic antiemetics

- One or two episodes of breakthrough emesis may not be ideal, but can reflect some efficacy of the original antiemetic regimen
    - Other agents can be added such as a benzodiazepine, prochlorperazine or haloperidol, or high dose intravenous metoclopramide
- Refractory emesis
    - Occurs after chemotherapy & after prophylactic antiemetic have failed in other courses of chemotherapy

- The most important factor determining the likelihood of acute or delayed emesis during chemotherapy is the intrinsic emetogenicity of the particular agent

- Chemotherapy agents were divided into 4 categories based upon the risk of emesis in the absence of antiemetic prophylaxis:
    - Highly emetogenic chemotherapy: > 90% risk of emesis
    - Moderately emetogenic chemotherapy: > 30-90% risk of emesis
    - Low emetogenic chemotherapy: 10-30% risk of emesis
    - Minimally emetic chemotherapy: < 10% risk of emesis

- For combination chemotherapy, the emetic level is determined by identifying the most emetic agent in the combination and then assessing the relative contribution of the other agents
    - Two moderately emetogenic agents when given together, can be highly emetic

- Most of the cancer regimens that are associated with delayed emesis are those that are highly emetogenic, although there are some moderately emetogenic agents that also cause delayed emesis

- There are 3 categories of drugs that are used in the management of CINV:
    - Selective 5-hydroxytryptamine type-3 receptor antagonists (5-HT3 RA)
        - 5-HT3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone (CTZ) of the area postrema
        - Chemotherapeutic agents produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine
        - Serotonin then activates 5-HT3 receptors located on vagal afferents to initiate the vomiting reflex
        - Available agents include:
            - Dolasetron – tabs, found in Anzemet
            - Granisetron – tabs, IV, SQ (as Sustol), transdermal (as Sancuso)
            - Ondansetron – ODT, tabs, film tabs (as Zuplenz), oral solution, IV
            - Palonostetron – IV, found in Aloxi & caps in combination with netupitant
    - Neurokinin-1 receptor antagonists (NK1RA)
        - Available agents
            - Aprepitant – caps, oral suspension (as Emend), IV emulsion (as Cinvanti)
            - Fosaprepitant – IV solution (as Emend)
            - Netupitant – caps in combination with palonostetron
            - Rolapitant – tabs (as Varubi), IV emulsion (as Varubi)
    - Glucocorticoids, especially dexamethasone

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- Short courses of glucocorticoids are widely used both as single agents for regimens with low risk of causing CINV and in combination with 5-HT3 RA and/or NK1RA for more emetic chemotherapy regimens

- Other agents that have been used in the treatment or prevention of CINV include dopaminergic antagonists such as phenothiazines (prochlorperazine), olanzapine, metoclopramide, and butyrophenones (haloperidol), as well as cannabinoids such as dronabinol
  - The benefits of synthetic oral cannabinoids in this setting remain controversial given the lack of evidence on their safety and efficacy
  - These agents have a lower therapeutic index than the 5-HT3 RA, NK1RA, and glucocorticoids for highly or moderately emetogenic chemotherapy regimens
  - There are studies that show adding olanzapine to NK1RA and 5-HT3RA resulting in substantial antiemetic activity
  - Their use should be restricted to patients who are intolerant of or refractory to these first-line agents

- Recommendations from the National Comprehensive Cancer Network (NCCN):
  - Doses and route of administration are dependent on agent(s) used
  - Regimens must start before chemotherapy (day-1)
    - Subsequent anti-emetics (days-2, 3, 4) depend on regimen chosen
  - High emetic risk chemotherapy, to prevent acute and delayed nausea and vomiting:
    - Any NK1RA + any 5-HT3 RA + dexamethasone
    - Olanzapine + palonosetron + dexamethasone
    - Aprepitant or fosaprepitant + any 5-HT3 RA + dexamethasone + olanzapine
  - Moderate emetic risk chemotherapy, to prevent acute and delayed nausea and vomiting:
    - A 2 or 3 drug combination may be used:
    - Any 5-HT3 RA + dexamethascone
    - Any NK1RA + any 5-HT3 RA + dexamethasone
    - Olanzapine + palonosetron + dexamethasone
  - Low emetic risk chemotherapy to prevent emesis:
    - Dexamethasone or metoclopramide or prochloperazine or 5-HT3 RA
  - Minimal emetic risk chemotherapy
    - No routine prophylaxis

AKYNZEO® (netupitant and palonosetron) oral capsule (cont.)

Definitions:

Emetogenicity of parenteral chemotherapeutic drugs (Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) Antiemetic Guideline 2016 March)

Level	Frequency of emesis (%)	Chemotherapeutic drug and dose
High	>90	Anthracycline/cyclophosphamide for breast cancer Carmustine Cisplatin Cyclophosphamide ≥1500 mg/m^2 Dacarbazine Mechlorethamine Streptozocin
Moderate	30 to 90	Alemtuzumab Azacytidine Bendamustine Carboplatin Clofarabine Cyclophosphamide <1500 mg/m^2 Cytarabine >1000 mg/m^2 Daunorubicin * Doxorubicin * Epirubicin * Idarubicin * Ifosfamide Irinotecan, liposomal irinotecan Oxaliplatin Romidepsin Temozolomide Thiotepa Trabectedin
Low ¶	10 to 30	Aflibercept Belinostat Blinatumomab Bortezomib Brentuximab Cabazitaxel Carfilzomib Catumaxumab Cetuximab Cytarabine ≤1000 mg/m^2 Docetaxel Eribulin Etoposide Fluorouracil Gemcitabine Ipilimumab

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		Ixabepilone Methotrexate Δ Mitomycin Mitoxantrone Paclitaxel and nab-paclitaxel Panitumumab Pegylated liposomal doxorubicin Pemetrexed Pertuzumab Temsirolimus Topotecan Ado-trastuzumab emtansine Vinflunine
Minimal ◊	<10	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Cladribine Fludarabine Nivolumab Ofatumumab Pembrolizumab Pixantrone Pralatrexate Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine

* These anthracyclines, when combined with cyclophosphamide, are designated as having high emetic risk.
¶ Another agent that is considered to be at low risk is daratumumab.
Δ At doses >1 gram, methotrexate has at least moderate emetogenic potential.
◊ Other agents that are considered to be minimal risk include cetuximab, elotuzumab, necitumumab, obinutuzumab, and olaratumab.

AKYNZEO® (netupitant and palonosetron) oral capsule (cont.)

Emetogenic potential of oral antineoplastic agents* (Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) Antiemetic Guideline 2016 March)

Degree of emetogenicity (incidence)	Agent
High (>90%)	Altretamine Procarbazine
Moderate (30 to 90%) ¶	Bosutinib Ceritinib Crizotinib Cyclophosphamide Imatinib Temozolomide Vinorelbine
Low (10 to 30%) Δ	Afatinib Axitinib Capecitabine Dabrafenib Dasatinib Etoposide Everolimus Fludarabine Ibrutinib Idelalisib Lapatinib Lenalidomide Nilotinib Olararib Pazopanib Ponatinib Regorafenib Sunitinib Tegafur uracil Thalidomide Vandetanib Vorinostat
Minimal (<10%)	Chlorambucil Erlotinib Gefitinib Hydroxyurea Melphalan Methotrexate Pomalidomide Ruxolitinib Sorafenib Thioguanine Vemurafenib Vismodegib

* Considerable uncertainty prevails for the emetogenic risk of oral agents.
¶ Other agents that are considered to be moderate risk include abemaciclib, busulfan (≥4 mg/day), cabozantinib, lomustine, niraparib, olaparib, ribociclib, and rucaparib.
Δ Other agents that are considered to be low risk include acalabrutinib, alectinib, bexarotene, brigatinib, cobimetinib, estramustine, ixazomib, lenvatinib, osimertinib, palbociclib, panobinostat, sonedegib, topotecan, trametinib, trifluridine-tipiracil, and venetoclax.

Akynzeo (netupitant/palonosetron)

Medication class:
Antiemetic, substance P/neurokinin 1 receptor antagonist and selective serotonin-3 (5-HT3) receptor antagonist

FDA-approved indication(s):
- 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 to be used with dexamethasone 12 mg given orally 30-minutes prior to chemotherapy
    - Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy

Recommended Dose:
- 1 capsule given approximately 1-hour prior to the start of chemotherapy
    - With highly emetogenic chemotherapy, including cisplatin-based chemotherapy give dexamethasone 12 mg orally 30-minutes prior to chemotherapy on day-1 and 8 orally once daily on days 2-4
    - With anthracyclines and cyclophosphamide based chemotherapy and chemotherapy not considered highly emetogenic, give dexamethasone 12 mg orally 30-minutes prior to chemotherapy on day-1

Maximum dosage
- Not stated

Available Dosage Forms:
- 300 mg netupitant / 0.5 mg palonosetron caps in a pack of 1 cap in 1 blister

Warnings, Precautions, and other Clinical Information:
- Avoid use in severe hepatic impairment (Child-Pugh Class C)
- Avoid use in severe renal impairment or end stage renal disease
- Serotonin syndrome has been reported alone and in particular when used with serotonergic drugs such as SSRIs, SNRIs, MAOIs, mirtazapine, tramadol, fentanyl, lithium, and others
- Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving palonosetron with or without known hypersensitivity to other 5-HT3 receptor antagonists
- Netupitant is a moderate inhibitor of CYP3A4, use caution with drugs metabolized by CYP3A4, the inhibitory effect may last for multiple days
- Netupitant is metabolized by CYP3A4, use with a strong CYP3A4 inducer can decrease the efficacy of Akynzeo
- Palonosetron is metabolized by CYP2D6 and to a lesser extent by CYP3A4 and CYP1A2

AKYNZEO® (netupitant and palonosetron) oral capsule (cont.)

- Woman who is breast feeding an infant or child should stop breast feeding
- Akynzeo is not indicated for nausea and vomiting not due to cancer chemotherapy, nausea and vomiting of pregnancy, hyperemesis gravidarum, prevention and/or treatment of postoperative nausea and vomiting

Criteria:

- **Criteria for initial therapy:** Akynzeo (netuptant and palonosetron) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is an Oncologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of cancer chemotherapy induced acute or delayed nausea and vomiting associated with initial and repeat courses of **highly emetogenic cancer chemotherapy**
4. To be used with dexamethasone
5. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use **ALL** the following preferred step therapy agents:
    - Preferred step therapy agents include:
        - Combination of granisetron or ondansetron with aprepitant

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Akynzeo (netuptant and palonosetron) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met :

1. Individual continues to be seen by an Oncologist
2. The condition has responded while on therapy
    - Response is defined as:
        - Nausea and vomiting are controlled
3. Individual has been adherent with the medication
4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Significant adverse effect such as:
        - Hypersensitivity reactions, including anaphylaxis
            - Signs and symptoms may include: hives over neck and face, itching, nasal congestion, difficulty breathing, swelling of lips, mouth, tongue or throat
        - Serotonin syndrome:

AKYNZEO® (netupitant and palonosetron) oral capsule (cont.)

- Signs and symptoms may include: mental status changes (agitation, hallucinations, delirium, and coma), autonomic instability (tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (nausea, vomiting, diarrhea)

5. There are no significant interacting drugs

Renewal duration: i.e. 30 tablets per month for 12 months

Resources:

Akynzeo. Package Insert. Revised by manufacturer 12/2015. Accessed 12/20/17.
Package Insert. Reference ID 3740363. Revised by manufacturer 4/2015. Accessed 12/10/15, 12/4/16.
Package Insert. Reference ID 3642902. Revised by manufacturer 10/2014. Accessed 12/03/14.

Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) Antiemetic Guideline 2016 March. http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_2016_v.1.2.pdf

NCCN Clinical Practice Guidelines in Oncology: Antiemesis. Version 02.2017, March 28, 2017. https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf

UpToDate: Prevention and treatment of chemotherapy-induced nausea and vomiting in adults. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/prevention-and-treatment-of-chemotherapy-induced-nausea-and-vomiting-in-adults?search=chemotherapy%20induced%20nausea%20and%20vomiting&source=search_result&selectedTitle=1~73&usage_type=default&display_rank=1

UpToDate: Pathophysiology and prediction of chemotherapy-induced nausea and vomiting. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/pathophysiology-and-prediction-of-chemotherapy-induced-nausea-and-vomiting?search=chemotherapy%20induced%20nausea%20and%20vomiting&source=search_result&selectedTitle=2~73&usage_type=default&display_rank=2

UpToDate: General characteristics of antiemetic drugs. Current through Nov 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/characteristics-of-antiemetic-drugs?search=chemotherapy%20induced%20nausea%20and%20vomiting&source=search_result&selectedTitle=4~73&usage_type=default&display_rank=4

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.