

Class Update with New Drug Evaluation: Antiemetics

Date of Review: January 2016

Generic Name: netupitant/palonosetron
rolapitant

End Date of Literature Search: September 2015

Brand Name (Manufacturer): Akynzeo® (Eisai)
Varubi™ (Tesarco, Inc.)

Dossiers Received: yes (Akynzeo®)/ no (Varubi™)

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The antiemetic drug class will be reviewed to determine if there is any relevant, updated evidence to be incorporated into the recommendations provided to the Oregon Health Plan (OHP). Evidence identified since the last review in November of 2014 will be included.

Research Questions:

1. What is the comparative efficacy and effectiveness of different antiemetic treatments in reducing nausea or vomiting (n/v) in patients with cancer, post-operatively, during pregnancy, or in patients with severe n/v who require rescue treatment (i.e., emergency department visit or hospitalization)?
2. What are the comparative harms of different antiemetic treatments used in patients with cancer, post-operatively, or during pregnancy?
3. Are there subpopulations of patients in which a particular antiemetic treatment would be more effective or associated with less harm?

Conclusions:

- There is insufficient new comparative effectiveness or comparative harms evidence for any given antiemetic indication.
- One new guideline for the management of chemotherapy-induced nausea and vomiting (CINV) from the National Comprehensive Cancer Network (NCCN) has been published.¹ Key recommendations from clinical practice guidelines include up to 3 days of an antiemetic for patients beyond length of the chemotherapy regimen or radiation.^{1,2}
- Low strength of evidence from one systematic review and meta-analysis demonstrated that neurokinin-1 (NK1) receptor antagonists (RA) may be effective in controlling post-operative nausea and vomiting (PONV). The majority of the evidence was for aprepitant 80 mg compared to placebo, which reduced post-operative nausea, 45.2% vs. 76.1% (RR 0.60, 95% CI 0.47 to 0.75, p<0.001) and vomiting, 3.8% vs. 21.1% (RR 0.13, 95% CI 0.04 to 0.37; p<0.001) based on 3 randomized controlled trials (RCTs) (n=224).³
- Low strength of evidence from one RCT found the fixed dose combination product NEPA (netupitant 300 mg/palonosetron 0.5 mg) (Akynzeo®) to be superior to palonosetron for complete response (i.e., no rescue treatment required and no emesis) during the delayed phase (25-120 hours) in patients who received moderate emetogenic chemotherapy (MEC), 76.9% vs. 69.5% (p=0.001), number needed to treat (NNT) of 14.⁴ Guideline revisions in 2011 changed the

chemotherapy regimen used in this study from a MEC designation to high emetogenic chemotherapy (HEC), providing evidence to support NEPA use in HEC. NEPA provided superior response rates compared to palonosetron for key secondary endpoints; complete response in the acute phase (0-24 hours), complete response in the overall phase (0-120 hours), no significant nausea overall and no emesis overall. External validity of this study is limited by the study participants being primarily female (98%) with breast cancer (97%).

- There is low strength of evidence from two additional trials that support the use of NEPA for MEC and HEC regimens in the acute and delayed phases in a more diverse population with a variety of malignant diseases.^{5,6} NEPA + dexamethasone was found to provide a complete response in 81-91% of patients, compared to 84-92% of patient taking a control regimen of aprepitant + palonosetron + dexamethasone, receiving six cycles of chemotherapy in a safety study.⁶ Evidence for the efficacy of oral palonosetron, in the acute phase after HEC, was demonstrated in a comparative trial of oral palonosetron compared to intravenous (IV) palonosetron. Complete response rates in the acute phase were higher for oral palonosetron 0.50 mg compared to IV palonosetron 0.25 mg, 76.3% vs. 70.4%.⁵
- There is insufficient data on the comparative effectiveness of the NK1 RA rolapitant (Varubi™). Currently, only prescribing information could be found.⁷

Recommendations:

- No changes are recommended to the PDL.
- Approve antiemetic PA as amended:
 - Patients who receive chemotherapy or radiation are allowed 3 days of antiemetic therapy beyond length of treatment.
 - Require PA for doxylamine/pyridoxine to cover for pregnancy-induced n/v after a failed trial of pyridoxine.
 - Require PA for NEPA and rolapitant.

Previous Conclusions and Recommendations:

- There is evidence that palonosetron may be superior to other 5HT3 antagonists for management of CINV due to moderately emetogenic chemotherapy; however, ondansetron, dolasetron, and granisetron are equally effective for CINV and PONV.⁸
- In pregnancy, ondansetron is not superior to promethazine for effectiveness but is less sedating. Long-term studies show no difference in number of live births, proportion of infant deformities, or birth weight between ondansetron and active control groups. There is low quality evidence that doxylamine/pyridoxine led to significantly greater improvement in n/v symptoms compared to placebo but there is insufficient comparative evidence with other antiemetic therapy.⁸
- Ondansetron is superior to granisetron for complete response rates in subpopulations with a predisposition to n/v, such as motion sickness or previous treatment with emetogenic chemotherapy.⁸
- No changes were recommended to the PMPDP.

Background:

Antiemetics are commonly prescribed for CINV, PONV, and pregnancy-related n/v. A multitude of medical conditions can also cause n/v which are often treated with promethazine, metoclopramide, prochlorperazine, and ondansetron.⁹ Risk factors for n/v are female gender, history of motion sickness, and non-smoking history.¹⁰ In addition to these risk factors, patients undergoing surgery are at increased risk if they have a previous history of PONV; receive post-operative opioids; receive general (versus regional) anesthesia, volatile anesthetics or nitric oxide; and certain types of surgery.^{10,11} Newer antiemetics used at minimal doses are well tolerated and are associated with a low incidence of adverse effects.¹¹ Important outcomes for evaluating effectiveness of antiemetics are incidence of n/v, need for rescue therapy and quality-of-life assessments. For CINV, the Functional Living Index-Emesis (FLIE) is used to determine the effect of

n/v on patients' daily lives. The Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status is also used to describe patient functioning (ability to care for them self, daily activities, and physical ability) on a scale of 1-5 (Table 1).¹²

Table 1. ECOG Scale of Performance Status¹²

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Pregnancy-related n/v requires treatment in 10% of females. Pyridoxine, a form of vitamin B6, is recommended as a first-line therapy by the American Congress of Obstetricians and Gynecologists (ACOG).¹³ The combination of pyridoxine with doxylamine, a first-generation antihistamine, is recommended for pregnant patients who fail pyridoxine alone. The 5HT3 receptor antagonists (RA) are frequently prescribed for pregnancy-related n/v, despite limited evidence to support their use.¹³

PONV occurs in 25-30% patients undergoing surgery and in up to 70-80% patients at high-risk who do not receive antiemetic prophylaxis.¹⁰ In addition, post-discharge nausea and vomiting (PDNV) occurs in 30-50% patients discharged from surgery.¹¹ Antiemetics recommended by the Society for Ambulatory Anesthesiology (SAA) recommend 5HT3 RA, NK1 RA, corticosteroids, butyrophenones (e.g., droperidol), antihistamines, and anticholinergics.¹¹ Patients at medium to high risk for PONV should receive one or two antiemetics to prevent PONV.¹¹ There is no evidence of clinically significant difference in effectiveness between antiemetics used for PONV and guidelines do not prefer one treatment over another.^{10,11,14}

CINV is highly dependent upon the chemotherapeutic agent used, dose of therapy, schedule and route of treatment. Radiation-induced nausea and vomiting (RINV) varies dependent upon area of the body and the amount exposed to treatment.¹ Patient variables, such as age, sex, prior chemotherapy, and alcohol use may also influence degree of CINV. Young female patients are at highest risk for CINV. Incidence of vomiting can be reduced by about 60% when prophylactic antiemetics are used; however, nausea is much more difficult to control. CINV is classified into acute (0-24 hours), delayed (24-170 hour), anticipatory, breakthrough or refractory.¹

Guidelines for CINV recommend antiemetic therapy based on emetogenic potential (Table 2).² Antiemetic regimens should be guided by the chemotherapeutic agent with the greatest emetic risk in the regimen.² In pediatric patients recommendations are the same for MEC and HEC regimens: a 5-HT3 RA plus a corticosteroid. For patients undergoing high-dose chemotherapy with stem cell or bone marrow transplant, a 5-HT3 RA with dexamethasone is recommended.² The addition of lorazepam, alprazolam or olanzapine may be considered in patients with breakthrough n/v. High-dose intravenous metoclopramide can be substituted for a 5HT3 RA or a dopamine antagonist can be considered. Lorazepam and diphenhydramine are only used as adjunctive therapy.²

Table 2. American Society of Clinical Oncology (ASCO) Guideline Recommendations for Antiemetics²

Regimen	Recommendation
<i>Highly Emetogenic Chemotherapy (HEC)</i>	- Three-drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone
<i>Moderately Emetogenic Chemotherapy (MEC)</i>	- Two-drug combination of palonosetron and dexamethasone - If palonosetron is not available, substitute a first generation 5-HT3 receptor antagonist, preferably granisetron or ondansetron - Limited evidence also supports adding aprepitant to the combination
<i>Low Emetogenic Chemotherapy</i>	- A single 8 mg dose of dexamethasone
<i>High-dose Chemotherapy</i>	- 5-HT3 antagonists and dexamethasone
<i>High-risk Radiation-induced nausea and vomiting</i>	- 5-HT3 antagonist before each fraction and 24 hours following and dexamethasone during fractions 1-5
<i>Moderate-risk Radiation-induced nausea and vomiting</i>	- 5-HT3 antagonist before each fraction and may consider dexamethasone during fractions 1-5
<i>Low-risk Radiation-induced nausea and vomiting</i>	- 5-HT3 antagonist alone as prophylaxis or rescue
<i>Minimal-risk Radiation-induced nausea and vomiting</i>	- Rescue therapy with a dopamine receptor antagonist or a 5-HT3 antagonist
<i>Multi-day chemotherapy</i>	- Antiemetics appropriate for emetogenic risk class of chemotherapy be given during treatment and for 2 days after

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:COCHRANE – Interventions for Nausea and Vomiting in Early Pregnancy

Studies in patients in early pregnancy with n/v and retching were reviewed. Both pharmacological and non-pharmacological therapies were included.¹⁵ Forty-one studies met inclusion criteria. Limited data suggested ginger products may be helpful but evidence was not consistent. Evidence for the use of pharmacotherapy was limited. Studies with vitamin B6, doxylamine-pyridoxine and other antiemetics were identified but pooling of the data was not possible due to heterogeneity of patients and interventions. Low-quality evidence for important outcomes prevent conclusions based on effectiveness of antiemetic treatments.¹⁵

Canadian Agency for Drugs and Technology in Health (CADTH)

CADTH released a rapid response review on the long-term use (>5 days) of ondansetron, dolasetron and granisetron in prevention of n/v in patients who are receiving chemotherapy or are postoperative.¹⁶ Literature was searched from January 1, 2009 to March 24, 2014. No evidence was found for long-term use of these agents.

Antiemetics for opioid-induced nausea was the focus of a second CADTH rapid response report.¹⁷ Nineteen studies met inclusion criteria for the review. Antiemetic drugs reviewed were found to be similar in effectiveness and combining antiemetics may improve outcomes. Both ondansetron and dimenhydrinate are recommended by guidelines for PONV.

Liu, et al – Neuorkinin-1 Receptor Antagonists in Preventing Postoperative Nausea and Vomiting

A systematic review and meta-analysis of NK-1 RA treatment was evaluated for PONV.³ Methodology followed PRISM guidelines and evidence was graded using a modified Jadad scale. The primary outcome of the review was the incidence of PONV. Complete response (defined as no need for rescue medication and absence of vomiting) was a secondary outcome. Treatments were evaluated 24 hours after surgery. Fourteen studies met inclusion criteria. NK-1 RAs included were the following: aprepitant, fosaprepitant, casopitant, ezlopitant, netupitant, rolapitant and vaestipitant.³ Evidence was found for aprepitant, rolapitant, and casopitant (not available in the US). Three RCTs including 224 patients found aprepitant to be effective for PONV versus placebo. Aprepitant 80 mg reduced post-operative nausea (RR 0.60, 95% CI 0.47 to 0.75, p<0.001) and vomiting (RR 0.13, 95% CI 0.04 to 0.37; p<0.001) compared to placebo. Aprepitant 40 mg was also superior to placebo for preventing incidence of vomiting. In a dose comparison study of aprepitant, there was no difference in efficacy between 80 mg and 125 mg doses (35% incidence of nausea for both groups). Aprepitant 40 mg and 125 mg doses were superior to ondansetron 4 mg at preventing n/v (RR 0.47, 95% CI 0.37 to 0.60; p<0.001 and RR 0.32, 95% CI 0.13 to 0.78; p=0.01, respectively).³ Incidence of vomiting was significantly reduced in a dose-dependent manner with rolapitant 20 mg, 70 mg and 200 mg doses compared to placebo. Significantly less patients were likely to require rescue therapy when they received 80 mg of aprepitant versus placebo; however, no difference was found in patients who received 40 mg of aprepitant versus placebo.³ No significance difference was found between ondansetron 4 mg and aprepitant 40 mg or 125 mg in requirement for rescue therapy or complete response rates. Limitations of the review include small sample size, inclusion of different surgery types, patients with varying susceptibility to PONV, and varying degrees of study quality.

New Guidelines:

NCCN Clinical Practice Guideline in Oncology

The NCCN guideline for use of antiemetics in supportive care in oncology was recently updated.¹ The NCCN guidelines are based on evidence and committee consensus. The primary treatment goal is prevention of CINV. Choice of antiemetic should be based on patient specific factors, emetic risk of chemotherapy, and prior antiemetic experience. Treatment recommendations based on chemotherapy are presented in Table 3.¹ Recommendations for intravenous HEC, MEC, LEC, oral chemotherapy regimens and RINV are based on low-quality evidence and consensus from the committee that the treatment is appropriate. The exceptions are for NK1 RA use in HEC regimens, which is supported by high-quality evidence and uniform consensus for use, and use of rolapitant, which is recommended for MEC based on high-quality evidence and uniform consensus for use. If breakthrough treatment is needed, an additional agent from a different class from the original regimen prescribed is recommended. Dexamethasone, 5HT3 RA, and IV palonosetron can be used for multi-day chemotherapy regimens. Aprepitant (with a 5HT3 RA and dexamethasone) and fosaprepitant (with dexamethasone) can also be used for multi-day HEC regimens.¹

Table 3. NCCN Guideline Recommendations for Antiemetics¹

Chemotherapy Regimen	Antiemetic Options - Day 1	Additional Antiemetic Therapy
<i>High Emetic IV Chemotherapy Agents</i>	1. NK1 RA (days 1-3) AND 5-HT3 RA AND dexamethasone	- Days 2-3: continue NK1 RA (exception is rolapitant which is given as one dose on day 1) AND - Days 2-4: continue dexamethasone
	2. NEPA AND dexamethasone	- Days 2-4: continue dexamethasone
	3. Olanzapine AND palonosetron IV AND dexamethasone	- Days 2-4: continue olanzapine
<i>Moderate Emetic IV Chemotherapy Agents</i>	1. 5-HT3 RA AND dexamethasone ± NK1 RA	- Days 2-3: 5HT3 RA OR dexamethasone OR NK1 RA with or without dexamethasone
	2. NEPA AND dexamethasone	- Days 2-3: continue dexamethasone
	3. Olanzapine AND palonosetron AND dexamethasone	- Days 2-3: continue olanzapine
<i>Low Emetic IV Chemotherapy Agents</i>	1. Dexamethasone OR 2. Metoclopramide OR 3. Prochlorperazine OR 4. 5HT3 RA	- Additional doses only if needed for breakthrough n/v
<i>High to Moderate Emetic Oral Chemotherapy</i>	1. 5HT3 RA	- Continue daily
<i>Low to Minimal Emetic Oral Chemotherapy</i>	1. As needed	- Continue daily if required
<i>Upper abdominal radiation (pretreatment)</i>	1. Ondansetron OR 2. Granisetron ± dexamethasone	- Additional only if needed for breakthrough n/v
<i>Total body irradiation (pretreatment)</i>	1. Ondansetron OR 2. Granisetron ± dexamethasone	- Additional only if needed for breakthrough n/v
<i>Multi-day Emetogenic Chemotherapy Regimens</i>	- Dependent upon chemotherapy regimen and emetogenic potential Options: • Dexamethasone for 2-3 days after chemotherapy • 5HT3 RA – frequency dependent on drug and	- Give antiemetic to cover both acute and delayed n/v

- route
- Palonosetron
- NK 1 RA for 2 days after chemotherapy

New Safety Alerts:

No new safety alerts identified.

New Formulations or Indications:

None identified.

Randomized Controlled Trials:

A total of 185 citations were manually reviewed from the literature search. After further review, four trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining four trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 4: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Oliveira, et al ¹³	Ondansetron 4 mg every 8 hours vs. pyridoxine 25mg plus doxylamine 12.5 mg every 8 hours x5 days	Pregnant females with n/v (n=36)	Improvement in nausea as reported on a 100-mm VAS	Ondansetron was associated with more improvement of baseline nausea compared to pyridoxine/doxylamine (median VAS decrease 51 mm vs. 20 mm, p=0.019).
Roila, et al ¹⁸	Dexamethasone 4 mg twice daily vs. aprepitant 80 mg once daily on days 2-3 after chemotherapy (All patients received IV palonosetron, dexamethasone and aprepitant before chemotherapy)	580 patients with breast cancer treated with anthracyclines plus cyclophosphamide	Rate of complete response (no vomiting or no rescue therapy) on day 2-5 after chemotherapy	Complete response rates were the same for both groups of antiemetic prophylaxis, 79.5%.
Kang H, et al ¹⁹	Aprepitant vs. control regimen (placebo for 3 days -All patients received ondansetron on day 1 and allowed use of dexamethasone	Children (6 mo. to 17 years) with malignancy and scheduled to receive MEC or HEC (n=307) during the delayed phase (25-120 h) after chemotherapy	Proportion who achieved complete response (no vomiting, no retching, and no use of rescue medication)	Aprepitant was superior to placebo during the delayed phase with 51% experiencing a complete response compared to 26%. Use of dexamethasone was similar between patients treated with aprepitant and the control regimen, 28% and 29%, respectively.

Schmitt T, et al ²⁰	<p>Aprepitant regimen vs. placebo control regimen</p> <p><u>Aprepitant regimen</u> Day 1: Aprepitant 125 mg + granisetron 2 mg + dexamethasone 4 mg Days 2-3: Aprepitant 80 mg + granisetron 2 mg + dexamethasone 2 mg Day 4: Aprepitant 80 mg + granisetron 2 mg</p> <p><u>Placebo regimen</u> Day 1: Placebo + granisetron 2 mg + dexamethasone 8 mg Days 2-3: Placebo + granisetron 2 mg + dexamethasone 4 mg Day 4: Placebo + granisetron 2 mg</p>	Patients (≥ 18 years) with multiple myeloma undergoing autologous transplant after high-dose melphalan conditioning (n=362)	No emesis and no rescue therapy within 120 hours of melphalan administration	Aprepitant was superior to control (OR 1.92, 95% CI 1.23 to 3.00; p=0.0042).
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NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Netupitant and Palonosetron (Akynzeo®)

Clinical Efficacy:

The fixed-dose combination product NEPA was approved in October of 2014 for the prevention of acute and delayed CINV associated with initial and repeat courses of chemotherapy, including HEC regimens.²¹ Palonosetron was previously approved in 2008 (but never marketed in the US) and netupitant is a new molecular entity.²² NEPA is administered as a single dose 1 hour before chemotherapy.⁴ FDA approval was based on four studies, three phase 3 studies and one phase 2 study.⁴⁻⁶ The phase 2 study did not meet our inclusion criteria.²³ The three phase 3 trials will be discussed below.

In a phase 3, double-dummy, double-blind randomized controlled trial a single oral dose of NEPA was compared to palonosetron 0.50 mg along with a dose of oral dexamethasone (12 mg for NEPA and 20 mg for palonosetron).⁴ All patients (n=1449) received MEC consisting of an anthracycline and cyclophosphamide. At the time of the study the chemotherapy regimen was considered moderately emetogenic, however, in 2011 ASCO guidelines recommended that this regimen now be considered highly emetogenic. Based on this change the FDA agreed that NEPA was appropriate for MEC and HEC regimens.²¹ Most patients were female (98%) with breast cancer (97%). The primary endpoint was complete response (defined as no emesis and no rescue medication) during the delayed phase (25-120 hours) in cycle 1. Secondary endpoints were complete response during the acute phase and incidence of emesis and “significant” nausea (not defined) during acute and delayed phases. The impact of CINV was assessed via FLIE.⁴

Results showed NEPA was superior to palonosetron alone for complete response during the delayed phase ($p=0.001$) with a number needed to treat (NNT) of 14. NEPA was also significantly better for complete response in the acute phase (0-24 hours) and overall phase (0-120 hours).⁴ NEPA demonstrated significantly higher FLIE scores compared to palonosetron, indicating that n/v had less impact on the daily lives of patients. Participants were invited to participate in a multiple-cycle extension study that has not yet been published.

A trial by Boccia, et al determined the noninferiority of oral palonosetron to IV palonosetron. The phase 3, double-blind, double-dummy randomized controlled trial compared a single dose of oral palonosetron 0.25 mg, 0.50 mg or 0.75 mg to IV palonosetron 0.25 mg in patients receiving MEC.⁵ Patients were also randomized to receive one dose of IV dexamethasone 8 mg or placebo. Patients were predominately females (63%) with breast cancer (82%) and a mean age of 57 years old. The primary endpoint was complete response during the acute phase (0-24 hours) with key secondary endpoints being complete response in the delayed phase (24-120) and the complete response overall (0-120).⁵ A complete response was defined as no emesis and no rescue therapy. During the acute phase all oral doses of palonosetron were noninferior to IV palonosetron, with a complete response percentage ranging from 70-76%. The palonosetron 0.50 mg oral dose was found to be noninferior to IV palonosetron 0.25 mg for the overall phase. None of the oral palonosetron doses achieved noninferiority to IV formulation for the delayed phase. The efficacy of the all the formulations was similar in the ability to prevent emesis and nausea. The addition of dexamethasone improved complete response rates by at least 15% for all groups during the acute phase, except for oral palonosetron 0.25 mg. These patients had an improvement of approximately 7% during the acute phase. Limitations to the study are the lack of details related to methodology, making the risk of bias unclear. The high percentage of females with breast cancer in the patient population limits the external validity.

In a safety study, NEPA was given in a phase 3, double-dummy, double-blind, randomized controlled trial to 413 chemotherapy naïve patients.⁶ NEPA day 1 was studied with aprepitant (125 mg on day 1, 80 mg days 2-3) + palonosetron (0.50 mg day 1) (AP) as a control. Both regimens were given with open label dexamethasone dose dependent on emetogenicity of chemotherapy regimen; 12 mg day 1 for MEC and 12 mg day 1 and 8 mg days 2-4 for HEC. No formal efficacy comparison was done. An equal number of males and females were enrolled and scheduled to receive multiple rounds of chemotherapy for a malignant tumor diagnosis. Seventy percent were prescribed a MEC regimen and patients had an ECOG performance status of 0-2. NEPA treated patients were found to have a higher number of poorer cancer prognostic variables compared to the AP study arm.⁶ A complete response (no emesis, no rescue medication) and no significant nausea were key efficacy endpoints. Treatment emergent adverse events and clinical evaluations were used for safety endpoints.

A complete response was seen in 81-91% of patients taking NEPA compared to 76-86% taking AP for chemotherapy cycles 1-6. Patients experienced no significant nausea in 84-92% patients taking NEPA and 81-87% of patients taking AP. This study provided a descriptive analysis of efficacy for NEPA in MEC and HEC regimens over multiple cycles. Limitations were that the focus of this study was safety, not efficacy, therefore, there was no formal efficacy comparison and patients had a variable cancer diagnoses and chemotherapy regimens.

Clinical Safety:

NEPA was well tolerated in short-term clinical studies (Table 5).²⁰ Constipation, erythema and dyspepsia was associated with NEPA in 3-4% of patients on a HEC regimen. A safety study in patients receiving multiple rounds of chemotherapy found no cardiac abnormalities with NEPA treatment.²⁰ One patient developed acute psychosis that was thought to be linked to NEPA. No other severe adverse events were seen. Less than 1% of patients in studies discontinued NEPA due to treatment related adverse events.^{4, 22}

Table 5. Adverse Reactions Occurring in ≥3% of Patients Receiving NEPA²⁰

Adverse Event	NEPA (n=725)	Palonosetron 0.50 mg (n=725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

Rolapitant (Varubi®)

Clinical Efficacy:

Rolapitant was approved in September 2015 to be used in combination with other antiemetic agents for the prevention of delayed CINV associated with initial and repeat courses of chemotherapy, including HEC regimens, in adults. Rolapitant 180 mg (2 tablets) is administered as a single dose 1-2 hours before chemotherapy with dexamethasone and a 5-HT₃ RA.⁷ No studies have been published and no trial results are available on Clinicaltrials.gov.

Prescribing information for rolapitant provides data from 2 RCTs.⁷ Studies 1 and 2 were double-blind, parallel-group RCTs (n=1,076) that compared rolapitant 180 mg to placebo in patients also on oral dexamethasone (20 mg on day 1 and 8 mg twice daily on days 2-4) and 10 mcg/kg IV granisetron. Rolapitant and placebo were given 1 to 2 hours prior to HEC (cisplatin, with 84% on an additional concomitant chemotherapy agents), and dexamethasone and granisetron were given 30 minutes prior to treatment on Day 1. The studies included 65% males and a mean age of 58 years. The primary endpoint was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25-120 hours).⁷ In study 1, complete response was seen in 72.7% of patients on rolapitant compared to 58.4% on placebo (95% CI 6.3 to 22.4; p<0.001). In study 2, a complete response occurred in 70.1% on rolapitant compared to 61.9% on placebo (95% CI 0.3 to 16.1; p=0.043).

Rolapitant was also studied in patients taking MEC regimens (n=1,369) with the same design as in Studies 1 and 2. Patients were randomized to rolapitant 180 mg or placebo on background oral granisetron 2 mg and oral dexamethasone 20 mg on Day 1. Oral granisetron 2 mg was also given on day 2 and 3. At least 50% of patients were on combination chemotherapy consisting of an anthracycline and cyclophosphamide. Included patients were a mean age of 57 years and 80% were female. The primary endpoint was the same as in studies 1 and 2. Rolapitant was superior to placebo in terms of complete response (71.3% vs. 61.6%, respectively; treatment difference 9.8; 95% CI 4.7 to 14.8; p<0.001).⁷

Clinical Safety:

In HEC regimens, rolapitant was more commonly associated with neutropenia and hiccups; in MEC, more decreased appetite, neutropenia and dizziness was observed.⁵

Table 6. Adverse Reactions Occurring in ≥3% of Patients Receiving Rolapitant on HEC Regimens⁷

Adverse Event	Rolapitant* (n=624)	Control (n=627)
Neutropenia	9%	8%
Hiccups	5%	4%
Abdominal Pain	3%	2%

* Rolapitant was given with dexamethasone and 5-HT3 receptor antagonist
Control therapy: placebo, dexamethasone and 5-HT3 receptor antagonist

Pharmacology and Pharmacokinetic Properties:

Parameter	Netupitant (N) and Palonosetron (P) ²⁰	Rolapitant ⁵
Mechanism of Action	P/neurokinin 1 (NK ₁) receptor antagonist and a serotonin-3 (5HT ₃) receptor antagonist	P/neurokinin 1 (NK ₁) receptor antagonist
Oral Bioavailability	97%	Not reported
Distribution and Protein Binding	Distribution is 8.3 ± 2.5 L/kg 62% protein bound	Vd: 460 L 99.8% protein bound
Elimination	86.5% feces and 4.7% urine	73% feces and 14.2% urine
Half-Life	N: 96 hours and P: 44 hours	169 to 183 hours
Metabolism	Predominately CYP2D6 and lesser extent CYP3A4 and CYP1A2	CYP3A4

Abbreviations: VD = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Vomiting
- 2) Nausea
- 3) Retching
- 4) Need for rescue medication
- 5) Quality of life

Primary Study Endpoint:

- 1) Complete Response (no emesis and no rescue medication)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Aapro, et al ⁴ Phase 3, PG, DB, DD, RCT	1. NEPA* 300mg/0.50 mg single oral dose + dexamethasone 12 mg single oral dose 2. Palonosetron (P) 0.5 mg single oral dose + dexamethasone 20 mg single oral dose *NEPA= netupitant 300mg and palonosetron 0.5 mg	Demographics: Female: 98% Age: 54 years White: 80% EGOG PS of 0: 70% Key Inclusion Criteria: - Age ≥ 18 years - Naïve to chemotherapy - Receiving first course of AC MEC - solid malignant tumor - ECOG status of 0-2 Key Exclusion Criteria: - HEC from day 1-5 - Additional MEC from day 2-5 following chemo - radiation to abdomen or pelvis - bone marrow or stem cell transplant - nausea or vomiting within 24 hours of day 1. - strong or moderate CYP3A4 inhibitors - Cardiac abnormalities	FAS: NEPA= 724 P=725 PP: NEPA= 719 (99%) P=719 (99%) Attrition: NEPA=7 (1%) P=10 (1%)	<u>Complete response during delayed phase:</u> NEPA 557 (76.9%) P 504 (69.5%) P=0.001	7.4/14	<u>Serious AE:</u> NEPA 13 (1.8%) P 12 (1.7%) p=NR <u>AE leading to D/C:</u> NEPA 0 (0%) P 2 (0.1%) p=NR <u>Headache:</u> N 24 (3.3%) P 22 (3.0%) p=NR	N/A	Risk of Bias (low/high/unclear): <u>Selection:</u> (unclear) No details on randomization provided. <u>Performance:</u> (low) Blinding maintained by double-dummy design. No details on patient or provider blinding. <u>Detection:</u> (unclear) No details provided on outcome assessment blinding. <u>Attrition:</u> (low) Low attrition; FAS used for efficacy analysis. Applicability: <u>Patient:</u> 98% female, 97% breast cancer; may limit applicability. However, young females are at highest risk of CINV, requiring triple therapy. <u>Intervention:</u> single dose appropriate. <u>Comparator:</u> Palonosetron; only demonstrates efficacy for netupitant. <u>Outcomes:</u> Outcome of complete response (no emesis and no rescue medication) appropriate. <u>Setting:</u> Conducted in 177 outpatient sites in 15 countries.
				<u>Complete response during acute phase:</u> NEPA 640 (88.4%) P 616 (85%) P=0.047	3.4/29			
				<u>Complete response during overall phase:</u> NEPA 538 (74.3%) P 483 (66.6%) P=0.001	7.7/13			
				<u>No emesis overall:</u> NEPA 578 (79.8%) P 523 (72.1%) P<0.001 <u>No significant nausea overall:</u> NEPA 540 (74.6%) P 501 (69.1%) P=0.020	7.7/13			
2. Boccia, et al ⁵ Phase 3, PG, DB, DD, RCT	1. Palonosetron 0.25 mg single oral dose (P25) 2. Palonosetron 0.50 mg single oral	Demographics: Female: 63% Age: 57 years Key Inclusion Criteria:	FAS: P25 = 157 P50 = 161 P75 =	<u>Complete response during acute phase:</u> P25 114 (73.5%) P50 122 (76.3%) P75 117 (74.1%) P 114 (70.4%)	NA	<u>AE leading to D/C:</u> P25 0 (0%) P50 1 (0.6%) P75 2 (1.3%) P 0 (0%) no p-value provided	NA	Risk of Bias (low/high/unclear): <u>Selection:</u> (unclear) No details on randomization provided. <u>Performance:</u> (low) Blinding maintained by double-dummy design. No details on patient or provider blinding.

	<p>dose (P50)</p> <p>3. Palonosetron 0.75 mg single oral dose (P75)</p> <p>4. Palonosetron 0.25 mg single IV dose (P)</p>	<p>- Age ≥ 18 years - Naïve or non-naïve to chemotherapy - Receiving MEC - malignant disease</p> <p><u>Key Exclusion Criteria:</u> - HEC - previous palonosetron use within the previous 2 weeks - irradiation to upper abdomen, cranium or total body days 1-5 - Low-level emetogenic chemotherapy - hepatic, renal or CV conduction interval abnormalities</p>	<p>158 P = 163</p> <p>PP: P25 = 155 (99%) P50 = 161 (100%) P75 = 157 (99%) P = 161 (99%)</p> <p><u>Attrition:</u> P25 = 2 (1%) P50 = 0 (0%) P75 = 1 (1%) P = 2 (1%)</p>	<p>no p-value provided</p> <p><u>Complete response during delayed phase:</u> P25 92 (59.4%) P50 100 (62.5%) P75 95 (60.1%) P 106 (65.4%) no p-value provided</p> <p><u>Complete response overall:</u> P25 83 (53.5%) P50 94 (58.8%) P75 84 (53.2%) P 96 (59.3%) no p-value provided</p>	<p>NA</p> <p>NA</p>	<p><u>Treatment related adverse events:</u> P25 11 (7%) P50 13 (8.1%) P75 12 (7.6%) P 26 (16.0%) no p-value provided</p>	<p><u>Detection</u> :(unclear) No details provided on outcome assessment blinding. <u>Attrition</u> :(low) Low attrition; FAS used for efficacy analysis.</p> <p>Applicability: <u>Patient:</u> A higher number of females and breast cancer diagnosis were represented in population. <u>Intervention:</u> oral palonosetron comparative doses appropriate. <u>Comparator:</u> IV Palonosetron; appropriate comparator for non-inferiority of oral product <u>Outcomes:</u> Outcome of complete response (no emesis and no rescue medication) appropriate. <u>Setting:</u> Conducted in 46 sites in 3 countries.</p>	
<p>3. Gralla, et al⁶</p> <p>Phase 3, PG, DB, DD, RCT, safety study</p>	<p>1. NEPA* 300mg/0.50 mg single oral dose + dexamethasone[∞] (NEPA)</p> <p>2. Aprepitant** + Palonosetron 0.50 mg on day 1 + dexamethasone[∞] (AP)</p> <p>*NEPA= netupitant 300mg and palonosetron 0.5 mg</p> <p>[∞] Dexamethasone was given open</p>	<p><u>Demographics:</u> Female: 50% Age: 58 years MEC: 76% HEC: 24% ECOG PS of 0: 48% ECOG PS of 1: 51%</p> <p><u>Key Inclusion Criteria:</u> - age ≥ 18 years - naïve to chemotherapy - scheduled to receive repeat courses of MEC or HEC chemotherapy - malignant tumor diagnosis -ECOG status of 0-2</p>	<p>FAS: NEPA= 309 AP = 104</p> <p>PP: NEPA= 198 (64%) AP = 61 (59%)</p> <p><u>Attrition:</u> NEPA= 111 (36%) AP=43 (41%)</p>	<p><u>Complete response over 6 cycles of chemotherapy:</u> NEPA 81-91% AP 76-86% p-value not calculated</p> <p><u>No significant nausea:</u> NEPA 84-92% AP 81-87% p-value not calculated</p>	<p>NA</p> <p>NA</p>	<p><u>Serious AE:</u> NEPA 1 (0.3%) APR 0 (0%) p=NR</p> <p><u>AE leading to D/C:</u> NEPA 1 (0.3%) APR 0 (0%) p=NR</p>	<p>N/A</p> <p>N/A</p>	<p>Risk of Bias (low/high/unclear): <u>Selection</u> :(unclear) Randomized 3:1. No details on randomization provided. <u>Performance:</u> (low) Blinding maintained by double-dummy design. No details on patient or provider blinding. <u>Detection</u> :(unclear) No details provided on outcome assessment blinding. <u>Attrition</u> :(high) High attrition; FAS used for efficacy analysis.</p> <p>Applicability: <u>Patient:</u> Men and women patients predominately treated with MEC (76%) and to a lesser extent with HEC (24%). <u>Intervention:</u> single dose appropriate. <u>Comparator:</u> Aprepitant; used as a control for safety study. <u>Outcomes:</u> Outcome of complete response (no emesis and no rescue medication) is appropriate.</p>

	<p>label and dose was dependent on emetogenicity of chemotherapy regimen: MEC – 12 mg day 1 HEC – 12 mg day 1 and 8 mg days 2-4</p> <p>** Aprepitant given as 125 mg on day 1, 80 mg on days 2-3</p>	<p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> - breast cancer diagnosis scheduled to receive anthracycline-cyclophosphamide HEC from day 1-5 - MEC or HEC on days 2-5 - bone marrow transplant or stem cell rescue - prior NK1 RA use - cardiac abnormalities - Drugs with CYP3A4 interactions 					<p><u>Setting:</u> Conducted in 59 sites in 10 countries.</p>
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AC= Anthracycline-cyclophosphamide; AE= adverse event; CINV= chemotherapy-induced nausea and vomiting; D/C = discontinuation; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FAS= full analysis set; HEC=highly emetogenic chemotherapy; MEC= moderately emetogenic chemotherapy; number needed to harm; NNT = number needed to treat; NR= not reported; PP = per protocol

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Appendix 1: Current Status on Preferred Drug List

Antiemetics, 5HT3 and Substance P Antagonists

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SOLUTION	ONDANSETRON HCL	ONDANSETRON HCL	Y
ORAL	SOLUTION	ZOFRAN	ONDANSETRON HCL	Y
ORAL	TAB RAPDIS	ONDANSETRON ODT	ONDANSETRON	Y
ORAL	TAB RAPDIS	ZOFRAN ODT	ONDANSETRON	Y
ORAL	TABLET	ONDANSETRON HCL	ONDANSETRON HCL	Y
ORAL	TABLET	ZOFRAN	ONDANSETRON HCL	Y
INTRAVEN	VIAL	EMEND	FOSAPREPITANT DIMEGLUMINE	N
ORAL	CAP DS PK	EMEND	APREPITANT	N
ORAL	CAPSULE	AKYNZEO	NETUPITANT/PALONOSETRON HCL	N
ORAL	CAPSULE	EMEND	APREPITANT	N
ORAL	FILM	ZUPLENZ	ONDANSETRON	N
ORAL	TABLET	ANZEMET	DOLASETRON MESYLATE	N
ORAL	TABLET	GRANISETRON HCL	GRANISETRON HCL	N
ORAL	TABLET DR	DICLEGIS	DOXYLAMINE/PYRIDOXINE HCL	N
TRANSDERM	PATCH TDWK	SANCUSO	GRANISETRON	N
ORAL	TABLET	VARUBI	ROLAPITANT	N

Appendix 2: Abstracts of Clinical Trials

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. *Annals of oncology* 2014; 25: 1328-1333.

BACKGROUND: Antiemetic guidelines recommend co-administration of agents that target multiple molecular pathways involved in emesis to maximize prevention and control of chemotherapy-induced nausea and vomiting (CINV). NEPA is a new oral fixed-dose combination of 300 mg netupitant, a highly selective NK1 receptor antagonist (RA) and 0.50 mg palonosetron (PALO), a pharmacologically and clinically distinct 5-HT₃ RA, which targets dual antiemetic pathways. **PATIENTS AND METHODS:** This multinational, randomized, double-blind, parallel group phase III study (NCT01339260) in 1455 chemotherapy-naïve patients receiving moderately emetogenic (anthracycline-cyclophosphamide) chemotherapy evaluated the efficacy and safety of a single oral dose of NEPA versus a single oral dose (0.50 mg) of PALO. All patients also received oral dexamethasone (DEX) on day 1 only (12 mg in the NEPA arm and 20 mg in the PALO arm). The primary efficacy end point was complete response (CR: no emesis, no rescue medication) during the delayed (25-120 h) phase in cycle 1. **RESULTS:** The percentage of patients with CR during the delayed phase was significantly higher in the NEPA group compared with the PALO group (76.9% versus 69.5%; $P = 0.001$), as were the percentages in the overall (0-120 h) (74.3% versus 66.6%; $P = 0.001$) and acute (0-24 h) (88.4% versus 85.0%; $P = 0.047$) phases. NEPA was also superior to PALO during the delayed and overall phases for all secondary efficacy end points of no emesis, no significant nausea and complete protection (CR plus no significant nausea). NEPA was well tolerated with a similar safety profile as PALO. **CONCLUSIONS:** NEPA plus a single dose of DEX was superior to PALO plus DEX in preventing CINV following moderately emetogenic chemotherapy in acute, delayed and overall phases of observation. As a fixed-dose antiemetic drug combination, NEPA along with a single dose of DEX on day 1 offers guideline-based prophylaxis with a convenient, single-day treatment.

Schmitt T, Goldschmidt H, Neben K, et al. Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: results of a randomized, placebo-controlled phase III trial. *J Clin Oncol* 2014;32:3413-3420.

PURPOSE: The optimal regimen to prevent chemotherapy-induced nausea and vomiting (CINV) for patients undergoing high-dose chemotherapy and autologous stem-cell transplantation (ASCT) is unclear. To evaluate the effect of aprepitant in addition to a standard regimen, we conducted this randomized, placebo-controlled phase III trial. **PATIENTS AND METHODS:** Patients with multiple myeloma were randomly assigned at a one-to-one ratio to receive either aprepitant (125 mg orally on day 1 and 80 mg orally on days 2 to 4), granisetron (2 mg orally on days 1 to 4), and dexamethasone (4 mg orally on day 1 and 2 mg orally on days 2 to 3) or matching placebo, granisetron (2 mg orally on days 1 to 4), and dexamethasone (8 mg orally on day 1 and 4 mg orally on days 2 to 3). Melphalan 100 mg/m² was administered intravenously on days 1 to 2. ASCT was performed on day 4. The primary end point (complete response) was defined as no emesis and no rescue therapy within 120 hours of melphalan administration. Quality of life was assessed by modified Functional Living Index-Emesis (FLIE) questionnaire on days -1 and 6. **RESULTS:** Overall, 362 patients were available for the efficacy analysis (181 in each treatment arm). Significantly more patients receiving aprepitant reached the primary end point (58% v 41%; odds ratio [OR], 1.92; 95% CI, 1.23 to 3.00; $P = .0042$). Absence of major nausea (94% v 88%; OR, 2.37; 95% CI, 1.09 to 5.15; $P = .026$) and emesis (78% v 65%; OR, 1.99; 95% CI, 1.25 to 3.18; $P = .0036$) within 120 hours was increased by aprepitant. Mean total FLIE score (\pm standard deviation) was 114 \pm 18 for aprepitant and 106 \pm 26 for placebo ($P < .001$). **CONCLUSION:** The addition of aprepitant resulted in significantly less CINV and had a positive effect on quality of life.

Kang H, Loftus S, Taylor A, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:385-94.

BACKGROUND: Oral aprepitant, a neurokinin-1 receptor antagonist, is recommended in combination with other anti-emetic agents for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy in adults, but its efficacy and safety in pediatric patients are unknown. We did this phase 3 trial to examine the safety and efficacy of such treatment in children. **METHODS:** In this final analysis of a phase 3, randomised, multicenter, double-blind study, patients aged 6 months to 17 years with a documented malignancy who were scheduled to receive either moderately or highly emetogenic chemotherapy were randomly assigned with an interactive voice response system to an age-based and weight-based blinded regimen of aprepitant (125 mg for ages 12-17 years; 3.0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12-17 years; 2.0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3, or placebo plus ondansetron on day 1 followed by placebo on days 2 and 3; addition of dexamethasone was allowed. Randomization was stratified according to patient age, planned use of chemotherapy associated with very high risk of emetogenicity, and planned use of dexamethasone as an anti-emetic. Ondansetron was dosed per the product label for pediatric use or local standard of care. The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25-120 h (delayed phase) after initiation of emetogenic chemotherapy. Efficacy and safety analyses were done with all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01362530. **FINDINGS:** Between Sept 22, 2011, and Aug 16, 2013, 307 patients were randomly assigned at 49 sites in 24 countries to either the aprepitant group (155 patients) or to the control group (152 patients). Three patients in the aprepitant group and two in the control group did not receive study medication, and thus were excluded from analyses. 77 (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase ($p < 0.0001$). The most common grade 3-4 adverse events were febrile neutropenia (23 [15%] of 152 in the aprepitant group vs 21 [14%] of 150 in the control group), anemia (14 [9%] vs 26 [17%]), and decreased neutrophil count (11 [7%] vs 17 [11%]). The most common serious adverse event was febrile neutropenia (23 [15%] patients in the aprepitant group vs 22 [15%] in the control group). **INTERPRETATION:** Addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients being treated with moderately or highly emetogenic chemotherapy.

Oliveira L, Capp S, You W, et al. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. *Obstet and Gynec* 2014; 124: 735-742.

OBJECTIVE: To evaluate whether ondansetron or the combination of doxylamine and pyridoxine was superior for the treatment of nausea and vomiting of pregnancy. **METHODS:** This was a double-blind, randomized, controlled trial in which women with nausea and vomiting of pregnancy were assigned to 4 mg of ondansetron plus a placebo tablet or 25 mg pyridoxine plus 12.5 mg of doxylamine for 5 days. The primary outcome was an improvement in nausea as reported on a 100-mm visual analog scale (VAS). Secondary outcomes were a reduction in vomiting on the VAS and the proportion of patients reporting sedation or constipation while using either study regimen. **RESULTS:** Thirty-six women (18 in each group) were randomized to either ondansetron or pyridoxine and doxylamine, of whom 13 (72%) and 17 (94%) completed follow-up, respectively. There were no differences among the groups with regard to demographic characteristics or baseline nausea. Patients randomized to ondansetron were more likely to have an improvement in their baseline nausea as compared with those using pyridoxine and doxylamine over the course of 5 days of treatment (median VAS score decreased 51 mm [interquartile range 37-64] compared with 20 mm [8-51]; $P = .019$). Furthermore, women using ondansetron reported less vomiting (median VAS decreased 41 [interquartile range 17-57] compared with

17 [-4 to 38]; $P=.049$). There was no significant difference between the groups regarding sedation or constipation. CONCLUSION: Our investigation showed ondansetron to be superior to the combination of pyridoxine and doxylamine in the treatment of nausea and emesis in pregnancy.

Roila F, Ruggeri B, Ballatori E, et al. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study. *J Clin Oncol* 2014; 32: 101-106.

PURPOSE: A combination of aprepitant, a 5-HT₃ receptor antagonist, and dexamethasone is recommended for the prophylaxis of acute or delayed emesis induced by chemotherapy containing anthracyclines plus cyclophosphamide in patients with breast cancer. The aim of this study was to verify whether dexamethasone is superior to aprepitant in preventing delayed emesis in patients receiving the same prophylaxis for acute emesis. **PATIENTS AND METHODS:** A randomized double-blind study comparing aprepitant versus dexamethasone was completed in chemotherapy-naïve patients with breast cancer treated with anthracyclines plus cyclophosphamide. Before chemotherapy, all patients were treated with intravenous palonosetron 0.25 mg, dexamethasone 8 mg, and oral aprepitant 125 mg. On days 2 and 3, patients randomly received oral dexamethasone 4 mg twice per day or aprepitant 80 mg once per day. Primary end point was rate of complete response (i.e., no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. **RESULTS:** Of 580 enrolled patients, 551 were evaluable: 273 received dexamethasone, and 278 received aprepitant. Day 1 complete response rates were similar: 87.6% for dexamethasone and 84.9% for aprepitant ($P < .39$). From days 2 to 5, complete response rates were the same with both antiemetic prophylaxes (79.5%; $P < 1.00$), as were results of secondary end points (i.e., complete protection, total control, no vomiting, no nausea, score of Functional Living Index-Emesis; $P < .24$). Incidences of insomnia (2.9% v 0.4%; $P < .02$) and heartburn (8.1% v 3.6%; $P < .03$) were significantly greater with dexamethasone on days 2 to 5. **CONCLUSION:** In patients with breast cancer treated with anthracycline plus cyclophosphamide chemotherapy and receiving the same antiemetic prophylaxis for acute emesis, dexamethasone was not superior to aprepitant but instead had similar efficacy and toxicity in preventing delayed emesis.

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AKYNZEO[®] safely and effectively. See full prescribing information for AKYNZEO[®].

AKYNZEO[®] (netupitant and palonosetron) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

AKYNZEO is a fixed combination of netupitant, a substance P/neurokinin 1 (NK₁) receptor antagonist, and palonosetron, a serotonin-3 (5-HT₃) receptor antagonist 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. Oral 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. (1)

DOSAGE AND ADMINISTRATION

One AKYNZEO capsule administered approximately 1 hour prior to the start of chemotherapy. (2)
AKYNZEO can be taken with or without food. (2)

DOSAGE FORMS AND STRENGTHS

Capsule: 300 mg netupitant/0.5 mg palonosetron (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving palonosetron with or without known hypersensitivity to other 5-HT₃ receptor antagonists (5.1)

- Serotonin syndrome has been reported with 5-HT₃ receptor antagonists alone but particularly with concomitant use of serotonergic drugs (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 3\%$ and greater than palonosetron) are headache, asthenia, dyspepsia, fatigue, constipation and erythema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai at 1-888-422-4743 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 Substrates:** inhibition of CYP3A4 by netupitant can result in increased plasma concentrations of the concomitant drug that can last at least 4 days and may last longer after single dosage administration of AKYNZEO; use with caution (7.1)
- CYP3A4 Inducers (e.g., rifampin):** decreased plasma concentrations of netupitant; avoid use (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment:** Avoid use in patients with severe hepatic impairment (8.6)
- Renal Impairment:** Avoid use in patients with severe renal impairment or end-stage renal disease (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VARUBI safely and effectively. See full prescribing information for VARUBI.

VARUBI™ (rolapitant) tablets, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

VARUBI™ is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 180 mg rolapitant administered approximately 1 to 2 hours prior to the start of chemotherapy (2)
- Administer in combination with dexamethasone and a 5-HT₃ receptor antagonist, see full prescribing information for dosing information (2)
- No dosage adjustment for dexamethasone is required. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg of rolapitant (3)

CONTRAINDICATIONS

Concurrent use with thioridazine, a CYP2D6 substrate (4)

WARNINGS AND PRECAUTIONS

Interaction with CYP2D6 Substrates with a Narrow Therapeutic Index: The inhibitory effect of a single dose of VARUBI on CYP2D6 lasts at least 7 days and may last longer. Avoid use of pimozide; monitor for adverse reactions if concomitant use with other CYP2D6 substrates with a narrow therapeutic index cannot be avoided (4, 5.1, 7.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are:

- Cisplatin Based Highly Emetogenic Chemotherapy: neutropenia and hiccups (6.1)
- Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide: decreased appetite, neutropenia and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tesaro at 1-844-4-TESARO or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- BCRP and P-gp Substrates with a Narrow Therapeutic Index: inhibition of BCRP and P-gp by VARUBI can increase plasma concentrations of the concomitant drug and potential for adverse reactions. See full prescribing information for specific examples. (7.1)
- Strong CYP3A4 Inducers (e.g., rifampin): significantly reduced plasma concentrations of rolapitant can decrease the efficacy of VARUBI; avoid use of VARUBI in patients who require chronic administration of such drugs. (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to September Week 2 2015

Search Strategy:

Database(s): Ovid MEDLINE(R) without Revisions 1996 to September Week 2 2015

Search Strategy:

#	Searches	Results
1	antiemetics.mp. or Antiemetics/	5652
2	neurokinin-1 receptor antagonist.mp. or Neurokinin-1 Receptor Antagonists/	1630
3	NEPA.mp.	52
4	netupitant.mp.	23
5	palonosetron.mp.	299
6	ondansetron.mp. or Ondansetron/	2664
7	aprepitant.mp.	530
8	fosaprepitant.mp.	40
9	dolasetron.mp.	242
10	granisetron.mp. or Granisetron/	1019
11	doxylamine.mp. or Doxylamine/	173
12	pyridoxine.mp. or Pyridoxine/	2293
13	rolapitant.mp.	5
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	11193
15	limit 14 to english language	10213
16	limit 15 to yr="2014 -Current"	612
17	limit 16 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	185

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.
- Restrict inappropriate chronic use (>3 days per week).
- For patients receiving chemotherapy or radiation, approve a quantity sufficient for 3 days beyond the duration of treatment.

Length of Authorization:

- Up to 6 months, or variable depending on chemotherapy (criteria specific)

Requires PA:

- Non-preferred drugs will be subject to PA criteria and quantity limits (**Table 1**)
- Preferred drugs will deny only when quantity limit exceeded

Table 1. Quantity Limits for Antiemetic Drugs.

Drug	Trade Name	Dose Limits
5-HT3 Receptor Antagonists		
Ondansetron	Zofran, Zuplenz, generic formulations	12 doses/ 7 days
Dolasetron	Anzemet	1 dose/ 7 days
Granisetron	Sancuso transdermal	1 patch / 7 days
	Generic oral	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists		
Aprepitant	Emend	3 doses/ 7 days
Rolapitant	Varubi	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists and 5-HT3 Receptor Antagonists Combinations		
Netupitant/palonosetron	Akynzeo	1 dose/ 7 days

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria

1. What is the diagnosis being treated?	Record ICD10 Code.
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2. Is the requested drug preferred?	Yes: Go to #4	No: Go to #3
3. Will the prescriber consider a change to the preferred product? Message: <ul style="list-style-type: none"> • Preferred products do not require a PA unless they exceed dose limits in table 1. • Preferred products do not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. 	Yes: Inform prescriber of covered alternatives in class and dose limits. If dose exceeds limits, continue to #4.	No: Go to #4
4. Is the request for doxylamine/pyridoxine (Diclegis®) for pregnancy-related nausea or vomiting?	Yes: Go to #5	No: Go to #6
5. Has the patient failed a trial of pyridoxine? Message: <ul style="list-style-type: none"> • Preferred vitamin B products do not require a PA. • Preferred products do not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. 	Yes: Approve for up to 3 months	No: Pass to RPh; deny and recommend a trial of pyridoxine.
6. Does the patient have a cancer	Yes: Approve for 3 days beyond length of	No: Go to #7

diagnosis and receiving chemotherapy or radiation?	chemotherapy regimen or radiation (not subject to dose limits above)	
7. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	Yes: Approve for up to 6 months	No: Go to #8
8. RPh only: All other indications need to be evaluated as to whether they are funded under the Oregon Health Plan. <input type="checkbox"/> Funded: Deny for medical appropriateness <input type="checkbox"/> Non-funded: Deny; not funded by the OHP		

P&T / DUR Review: 1/16 (KS); 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03
Implementation: TBD; 1/1/15; 1/1/14; 1/1/10; 7/1/06; 3/20/06; 6/30/04; 3/1/04; 6/19/03; 4/1/03