Class Update with New Drug Evaluation: Antiemetics

Date of Review: November 2015
Generic Name: netupitant/palonosetron rolapitant
End Date of Literature Search: 
Brand Name (Manufacturer): Akynzeo® (Eisai)
Varubi™ (Tesaro, Inc)
Dossiers Received: no

Current Status of PDL Class: See Appendix 1.

Purpose for Class Update:
The antiemetic drug class will be reviewed for updated evidence to incorporate 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 and vomiting in patients with cancer, postoperatively, pregnancy or severe nausea or vomiting (requiring hospitalization or emergency room treatment)?
2. What are the comparative harms of different antiemetics in patients with cancer, who are postop, pregnant or severe nausea and vomiting?
3. Are there subpopulations of patients with requiring an antiemetic for which one treatment would be more effective or associated with less harm?

Conclusions:
- There is insufficient new comparative effectiveness evidence or comparative harms between antiemetic agents for a given indication.
- One new guideline for the management of chemotherapy induced nausea and vomiting (CINV) from the National Comprehensive Cancer Network (NCCN) has been published. Key recommendations follow the American Society of Clinical Oncology (ASCO) guidance with the exception of recommending antiemetic therapy for up to 4 days for highly emetogenic chemotherapy (HEC) compared to 3 days.\(^1\)\(^,\)\(^2\)
- Low strength of evidence from one systematic review and meta-analysis demonstrated that neurokinin-1 (NK1) receptor antagonists (RA) were effective in controlling post-operative nausea and vomiting (PONV). The majority of the evidence was for aprepitant 80 mg, which was shown to reduce 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) based on 3 randomized controlled trials (n=224).\(^3\)
- Low strength of evidence from one randomized controlled trial found the fixed dose combination product NEPA (netupitant 300mg and palonosetron 0.5 mg) (Akynzeo\(^\ª\)) to be superior (p=0.001) to palonosetron alone in complete response (no rescue treatment and no emesis) during the delayed phase (25-120 hours) in patients taking a moderate emetogenic chemotherapy (MEC) regimen.\(^4\)

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Date: November 2015
There is insufficient data on the comparative effectiveness of the newly approved neurokinin 1 (NK1) receptor antagonist (RA), rolapitant (VARUBI™). Currently only prescribing information is available.5

Recommendations:
- Ondansetron is the recommended agent on the PDL. No changes are recommended to the PDL based on review of the clinical data. Evaluate costs in executive session.
- Recommend that patients meeting PA criteria requirement are allowed 4 days of antiemetic therapy.
- Recommend that doxylamine/pyridoxine be added to the Antiemetic PA criteria (Appendix 5).
- Recommend that NEPA and rolapitant be added to the Antiemetic PA criteria.

Previous Conclusions:
- There is evidence that palonosetron may be superior to RA in the treatment of chemotherapy induced nausea and vomiting for moderately emetogenic chemotherapy and that ondansetron, dolasetron, and granisetron are equally effective.2,7 There is low quality evidence that the combination of doxylamine/pyridoxine led to significantly greater improvement in nausea vomiting symptoms as compared with placebo (-4.8 PUQE score vs. -3.9; p=0.006) but insufficient comparative evidence compared to other available agents. Maintain as non-preferred.8
- Evaluate comparative costs in executive session.

Previous Recommendations:
- Ondansetron is the recommended agent on the PMPDP. No changes were recommended to the PMPDP.
- Costs were evaluated in executive session.

Background:
Antiemetics are commonly prescribed for nausea and vomiting caused by chemotherapy, post-operatively, and pregnancy. A multitude of medical conditions can also cause nausea and vomiting which are often treated with promethazine, metoclopramide, prochlorperazine, and ondansetron.9 Risk factors for nausea and vomiting are female gender, 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, postoperative opioids, general versus regional anesthesia, use of volatile anesthetics and nitric oxide, and surgery type.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 nausea and vomiting, need for rescue therapy and quality of life assessments. For CINV, the Functional Living Index-Emesis (FLIE) is used to determine the effect of nausea and vomiting in patients’ daily lives.

Pregnancy-induced nausea and vomiting requires treatment in 10% of females. Monotherapy treatment with pyridoxine is recommended as a first line therapy by the American Congress of Obstetricians and Gynecologists (ACOG).12 The combination of pyridoxine and doxylamine is recommended for pregnant patients who fail pyridoxine. 5HT3 RAs are frequently prescribed for nausea and vomiting in pregnancy, despite limited evidence to support its use.12

PONV occurs in 25-30% in patients undergoing surgery and in up to 70-80% in patients at high-risk who do not receive prophylaxis.10 Post-discharge nausea and vomiting (PDNV) is also problematic with 30-50% of patients experiencing PDNV.11 Antiemetics recommended by the Society for Ambulatory Anesthesiology

Author: K. Sentena, Pharm.D. Date: November 2015
Recommendation

(SAA) recommend 5HT3 RA, NK1 RA, corticosteroids, butyrophenones, antihistamines, and anticholinergics. Patients at medium to high risk should receive one to two interventions to prevent PONV. The difference in effectiveness of antiemetics used for PONV hasn’t been shown to be clinically significant and therefore guidelines do not preference one treatment over another.

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

Guidelines for CINV recommend antiemetic therapy based on emetogenic potential (Table 1). In combination chemotherapy regimens and patients also undergoing radiation, antiemetic regimens should be guided by the agent with the greatest emetic risk. In pediatric patients recommendations are the same for MEC and HEC regimens; 5-HT3 RA plus a corticosteroid. For patients undergoing high-dose chemotherapy with stem-cell or bone marrow transplant the recommendation is for a 5-HT3 receptor antagonist and dexamethasone. Preference is given to aprepitant based on limited evidence. The addition of lorazepam, alprazolam or olanzapine may be considered for patients with breakthrough emesis or nausea. High-dose IV metoclopramide can be substituted for 5HT3 RA or by adding a dopamine antagonist can also be considered. Lorazepam and diphenhydramine can also be used as adjunctive therapy, but not as single agents.

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

Table 1. ASCO Guideline Recommendations for Antiemetics

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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 nausea, vomiting and retching were reviewed. A multitude of interventions were included including pharmacological and non-pharmacological therapies.\(^{14}\) 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 findings was not possible due to heterogeneity of patients and interventions. Low-quality evidence prevented effectiveness conclusions for antiemetic treatments on important outcomes.\(^{14}\)

Canadian Agency for Drugs and Technology in Health (CADTH)
In April of 2014, CADTH released a rapid response review on the long-term use (>5 days) of ondansetron, dolasetron and granisetron in preventing nausea and vomiting in patients who are receiving chemotherapy or are postoperative.\(^{15}\) Literature was searched from January 1, 2009 to March 24, 2014. No evidence was found on long-term use of these agents.

Antiemetics for opioid-induced nausea was the focus of a second CADTH rapid response report released in August of 2014.\(^{16}\) Nineteen studies met inclusion criteria for the review. Antiemetic drugs reviewed were found to be similar in effectiveness and combining antiemetics appears to 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
In a recent systematic review and meta-analysis NK-1 RA were 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 (no need for rescue medication and absence of vomiting) was a secondary outcome. Outcomes comparisons were at 24 hours after surgery. Fourteen studies met inclusion criteria. NK-1 RAs included in the search were the following: aprepitant, fosaprepitant, casopitant, ezlopitant, netupitant, rolapitant and vaestipitant.\(^{3}\) Evidence was found for aprepitant, casopitant (not available in the US) and rolapitant. Three randomized controlled trials, including 224 patients, found aprepitant to be effective for PONV. Placebo comparisons from these trials found aprepitant 80 mg to reduce post-op 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). Two other studies found aprepitant 40 mg to be superior to placebo for incidence of vomiting. In a dose comparison study of aprepitant, 80 mg and 125 mg were found to demonstrate no difference in efficacy (35% incidence of nausea for both groups). Aprepitant 40 mg was found to be superior to

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ondansetron 4 mg (RR 47, 95% 0.37 to 0.60; p<0.001).\(^3\) Results were similar for the 125 mg dose of aprepitant compared to ondansetron 4 mg (RR 0.32, 95% CI 0.13 to 0.78; p=0.01). Incidence of vomiting was significantly reduced in a dose-dependent manner with rolapitant 20 mg, 70 mg and 200 mg compared to placebo. In a comparison of rescue drug use in patients taking aprepitant compared to placebo, significantly less patients were less likely to require rescue therapy in the 80 mg aprepitant group, however, no difference was found for the 40 mg group.\(^3\) No significance difference was found between ondansetron 4 mg and aprepitant 40 mg and 125 mg in requirement for rescue therapy or complete response rates. Small sample size, inclusion of different surgery types, different levels of susceptibility to PONV, and varying degrees of study quality are limitations of this review.

New Guidelines:
NCCN Clinical Practice Guidelines in Oncology

NCC guidelines on using antiemetics for supportive care in oncology patients were updated in February 2015.\(^1\) Guidelines are based on evidence and committee consensus. Goals of treatment are to prevent nausea and vomiting using therapy that lasts for duration of CINV, usually up to 4 days. Choice of antiemetic should be based on patient specific factors, emetic risk of chemotherapy, and prior antiemetic experience. Treatment recommendations for antiemetic class are presented in Table 3.\(^1\) All recommendations for IV HEC, IV MEC, IV LEC, oral regimens and radiation-induced nausea and vomiting (RINV) are based on low-level of evidence and uniform consensus from the committee that the treatment is appropriate. The exceptions are for the NK1 RA use in HEC regimens, which is supported by high-quality evidence and uniform consensus for use. For MEC the use of rolapitant is recommended based on high-quality evidence and uniform consensus for use. If breakthrough treatment is required it is recommended that an additional agent from a different class from original regimen be prescribed. Dexamethasone, 5HT3 RA, and IV palonosetron can be used for multiday chemotherapy regimens. Aprepitant (with a 5HT3 RA and dexamethasone) and fosaprepitant (with dexamethasone) can also be used for multiday HEC regimens.\(^1\)

Table 3. NCCN Guideline Recommendations for Antiemetics\(^1\)

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Antiemetic Day 1</th>
<th>Additional Antiemetic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Emetic IV Chemotherapy Agents</strong></td>
<td>- Three–drug combination of an NK1 RA (days 1-3), a 5-HT3 RA and dexamethasone on day 1 OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- NEPA and dexamethasone OR</td>
<td>- Continue NK1 RA, aprepitant and fosaprepitant, on days 2 and 3 (rolapitant is only one dose)</td>
</tr>
<tr>
<td></td>
<td>- Olanzapine, palonosetron IV and dexamethasone</td>
<td>- Dexamethasone is recommended on days 2-4 if NK1 RA, 5HT3 RA or NEPA used on day 1</td>
</tr>
<tr>
<td></td>
<td>- Optional therapy includes lorazepam on days 1-4 or an H2 blocker</td>
<td>- Rolipitant is only used on day 1. Give dexamethasone on day 2-4 if using (rolapitant regimen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- In olanzapine containing regimen use daily dose on days 2-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- SHT3 RA or dexamethasone on days 2-3 or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- NK1 RA, aprepitant and fosaprepitant with or without dexamethasone on day 2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rolipitant is only used on day 1. Give dexamethasone on day 2-3 if using (rolapitant regimen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If NEPA is used on day 1, use dexamethasone on days 2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- In olanzapine containing regimens, use daily olanzapine</td>
</tr>
</tbody>
</table>

Author: K. Sentena, Pharm.D.  
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<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Treatment Options</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Emetic IV Chemotherapy Agents</strong></td>
<td>On days 2-3 a NK1 receptor antagonist, dexamethasone or 5-HT3 receptor antagonist</td>
<td>on days 2-3</td>
</tr>
<tr>
<td></td>
<td>and optional therapy includes lorazepam on days 2-3 or an H2 blocker</td>
<td></td>
</tr>
<tr>
<td><strong>High to Moderate Emetic Oral Chemotherapy</strong></td>
<td>A single dose of dexamethasone, metoclopramide, prochlorperazine or 5HT3 RA</td>
<td>Additional only if needed for breakthrough nausea and vomiting</td>
</tr>
<tr>
<td><strong>Low to Minimal Emetic Oral Chemotherapy</strong></td>
<td>5HT3 RA</td>
<td>Continue daily</td>
</tr>
<tr>
<td><strong>Upper abdominal radiation (pretreatment)</strong></td>
<td>Ondansetron or granisetron</td>
<td>Additional only if needed for breakthrough nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Optional dexamethasone</td>
<td></td>
</tr>
<tr>
<td><strong>Total body irradiation (pretreatment)</strong></td>
<td>Ondansetron or granisetron</td>
<td>Additional only if needed for breakthrough nausea and vomiting</td>
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<tr>
<td></td>
<td>Optional dexamethasone</td>
<td></td>
</tr>
<tr>
<td><strong>Multi-day Emetogenic Chemotherapy Regimens</strong></td>
<td>Dependent upon chemotherapy regimen and emetogenic potential</td>
<td>Give antiemetic to cover both acute and delayed nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Options:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone for 2-3 days after chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 5HT3 RA – frequency and need for repeated administration is dependent upon drug and route</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IV Palonosetron</td>
<td></td>
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<tr>
<td></td>
<td>• NK 1 RA for 2 days after chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

**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, 4 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>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Quality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliveira, et al(^{12})</td>
<td>Ondansetron 4 mg vs. pyridoxine 25 mg plus doxylamine 12.5 mg for a total of 5 days</td>
<td>Pregnant females with nausea and vomiting (n=36)</td>
<td>Improvement in nausea as reported on a 100-mm visual analog scale (VAS)</td>
<td>Ondansetron was associated with more improvement of baseline nausea compared to pyridoxine/doxylamine (median VAS decrease 51 mm vs. 20 mm, (p=0.019))</td>
<td>Fair</td>
</tr>
<tr>
<td>Roila, et al(^{17})</td>
<td>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)</td>
<td>580 patients with breast cancer treated with anthracyclines plus cyclo-phosphamide</td>
<td>Rate of complete response (no vomiting or no rescue therapy) on day 2-5 after chemotherapy</td>
<td>Complete response rates were the same for both groups of antiemetic prophylaxis, 79.5%.</td>
<td>Fair</td>
</tr>
<tr>
<td>Kang H, et al(^{18})</td>
<td>Aprepitant vs. control regimen (placebo)* for 3 days *All patients received ondansetron on day 1 - All patients were allowed to use dexamethasone</td>
<td>Children (6 mo to 17 years) with malignancy and scheduled to receive MEC or HEC (n=307) during the delayed phase (25-120h) after chemotherapy</td>
<td>Proportion of patients achieving complete response (no vomiting, no retching, and no use of rescue medication)</td>
<td>Aprepitant was found to be superior to control during the delayed phase with 51% experiencing a complete response compared to 26% in the control group.</td>
<td>Good</td>
</tr>
<tr>
<td>Schmitt T, et al(^{19})</td>
<td>Aprepitant regimen vs. placebo control regimen Aprepitant regimen 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 Placebo regimen Day 1: Placebo + granisetron 2 mg + dexamethasone 8 mg Days 2-3: Aprepitant 80 mg + granisetron 2 mg + dexamethasone 4 mg Day 4: Placebo + granisetron 2 mg</td>
<td>Patients (≥ 18 years) with multiple myeloma undergoing autologous transplant after high-dose melphalan conditioning (n=362)</td>
<td>No emesis and no rescue therapy within 120 hours of melphalan administration</td>
<td>Aprepitant was found to be superior to control (OR 1.92, 95% CI 1.23 to 3.00; (p=0.0042))</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Abbreviations:
*Quality of each study is ranked as “Good”, “Fair” or “Poor” based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

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 combination product netupitant and palonosetron (NEPA) was approved in October of 2014 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, included by not limited to, HEC regimens. The oral palonosetron component helps to prevent nausea and vomiting during the acute phase and netupitant is effective in both the acute and delayed phase after cancer chemotherapy. NEPA is given as a single dose an hour before chemotherapy, without regard to food. Palonosetron was previously approved in 2008 and netupitant is a new molecular entity. Three main studies were submitted to gain FDA approval. One study is a phase III efficacy study, which will be discussed below.4 A study by Gralla et al, is a safety and efficacy study with no formal efficacy comparison and the third study is a phase II dose-ranging study by Hesketh, et al. The Gralla and Hasketh studies do not meet our inclusion criteria.

In the published study by Aapro, et al, netupitant 300 mg as a single oral dose and palonosetron 0.50 mg as a single oral dose were compared to a single oral dose of palonosetron 0.50 mg alone (n=1449).4 On day one, both treatment arms also received a dose of dexamethasone 12mg and 20 mg for NEPA and palonosetron, respectively. All patients received a MEC chemotherapy regimen consisting of anthracycline and cyclophosphamide. A majority of patients were female (98%) and had breast cancer (97%). The primary endpoint was complete response (no emesis and no rescue medication) during the delayed phase (25-120h) in cycle 1. Secondary endpoints were complete response during acute phase and emesis and significant nausea during acute and delayed phases. The impact of CINV was assessed via the Functional Living Index-Emesis (FLIE).4

Results from this study showed NEPA to be superior to palonosetron for complete response during the delayed phase, p=0.001. NEPA was also significantly better for complete response in the acute phase (0-24h) and overall (0-120h).4 NEPA demonstrated significantly higher FLIE scores compared to palonosetron, indicating less of an impact of nausea and vomiting on the daily lives of patients.

Clinical Safety:
NEPA was well tolerated in short-term clinical studies (Table 2). 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. 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

Author: K. Sentena, Pharm.D. Date: November 2015
Table 2. Adverse Reactions Occurring in ≥3% of Patients Receiving NEPA

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NEPA (n=725)</th>
<th>Palonosetron 0.50 mg (n=725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Rolapitant (Varubi®)

Clinical Efficacy:
Rolapitant was approved in September to be used in combination with other antiemetic agents 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 in adults. Rolapitant 180 mg (2 tablets) is given 1 to 2 hours prior to start of chemotherapy and is to be administered with dexamethasone and a 5-HT3 receptor antagonist. No studies have been published and no trial results are available on Clinicaltrials.gov.

Rolapitant package insert provides data from two clinical trials. Studies 1 and 2 were double-blind, parallel group studies, randomized controlled trials comparing 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 chemotherapy and dexamethasone and granisetron were given 30 minutes prior to treatment on Day 1. The combined population from both studies was 1,076 and included approximately 65% males and mean age of 58. All patients were on a HEC regimen. Patients received cisplatin and 84% were on a concomitant chemotherapy agent. The primary endpoint was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25-120h). In both studies, rolapitant was found to be superior to control therapy. In study 1, complete response was seen in 72.7% of patients on rolapitant compared to control 58.4% (95% CI 6.3 to 22.4; p<0.001). In study 2, similar results were seen with a complete response in 70.1% in the rolapitant group compared to 61.9% in the control group (95% CI 0.3 to 16.1; p=0.043). Rolapitant was also studied in patients taking MEC regimens (n=1369) 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 20mg on Day 1. Two mg of oral dexamethasone was given on day 2 and 3. At least 50% of patients were on combination chemotherapy consisting of anthracycline and cyclophosphamide. Included patients were a mean age of 57 with 80% being female. The primary endpoint was the same as in studies 1 and 2. Rolapitant was found to be superior to placebo with a complete response in 71.3% compared to 61.6% in the control group (95% CI 4.7 to 14.8; p<0.001).

Clinical Safety:
In HEC regimens, rolapitant was most commonly associated with neutropenia and hiccups and in MEC decreased appetite, neutropenia and dizziness.
Table 2. Adverse Reactions Occurring in ≥3% of Patients Receiving Rolapitant on HEC Regimens

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rolapitant* (n=624)</th>
<th>Control (n=627)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Hiccups</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3%</td>
<td>2%</td>
</tr>
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</table>

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

Pharmacology and Pharmacokinetic Properties:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Netupitant (N) and Palonosetron (P)</th>
<th>Rolapitant*</th>
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<td>Mechanism of Action</td>
<td>P/neurokinin 1 (NK₁) receptor antagonist and a serotonin-3 (5HT₃) receptor antagonist</td>
<td>P/neurokinin 1 (NK₁) receptor antagonist</td>
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<tr>
<td>Oral Bioavailability</td>
<td>97%</td>
<td>Not reported</td>
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<td>Distribution and Protein Binding</td>
<td>Distribution is 8.3 ± 2.5 L/kg</td>
<td>Vd: 460 L</td>
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<tr>
<td>Elimination</td>
<td>62% protein bound</td>
<td>99.8% protein bound</td>
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<tr>
<td>Half-Life</td>
<td>N: 96 hours and P: 44 hours</td>
<td>73% feces and 14.2% urine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Predominately CYP2D6 and lesser extent CYP3A4 and CYP1A2</td>
<td>169 to 183 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

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)
<table>
<thead>
<tr>
<th>Ref./Study Design</th>
<th>Drug Regimens/Duration</th>
<th>Patient Population</th>
<th>N</th>
<th>Efficacy Endpoints</th>
<th>ARR/NNT</th>
<th>Safety Outcomes</th>
<th>ARR/NNH</th>
<th>Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns</th>
</tr>
</thead>
</table>
| 1. Aapro, et al*  | 1. NEPA* (N) 300mg/0.50 mg single oral dose + dexamethasone 12 mg single oral dose 2. Palonosetron (P) 0.50 mg single oral dose + dexamethasone 20 mg single oral dose | Demographics:  
- Female: 98%  
- Age: 54 years  
- White: 80%  
Key Inclusion Criteria:  
- Age ≥ 18 years  
- Naive 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: N 724  
P 725  
PP: N 719 (99%)  
P 719 (99%)  
| Complete response during delayed phase:  
- N 557 (76.9%)  
- P 504 (69.5%)  
RR (95% CI, x to x)  
P=0.001  
Complete response during acute phase:  
- N 640 (88.4%)  
- P 616 (85%)  
RR (95% CI, x to x)  
P=0.047  
No emesis overall:  
- N 578 (79.8%)  
- P 523 (87.3%)  
P<0.001  
No significant nausea overall:  
- N 540 (74.6%)  
- P 501 (69.1%)  
P=0.020  
| Serious AE:  
- N 13 (1.8%)  
- P 12 (1.7%)  
p-value NR  
Adverse event leading to discontinuation:  
- N 0 (0%)  
- P 2 (0.1%)  
p-value NR  
Headache:  
- N 24 (3.3%)  
- P 22 (3.0%)  
p-value NR  
| Internal Validity (Risk of Bias):  
Selection: No details on randomization were provided.  
Performance: Blinding was maintained by double-dummy design. No details on patient or provider blinding.  
Detection: No details were provided on outcome assessment blindign.  
Attrition: Low attrition (1%) in each group. Full analysis set was used for efficacy analysis.  
Applicability:  
Patient: Ninety-eight percent of the populations were females and 97% had breast cancer, which limits applicability of findings to men and other cancers. However, young females are at the highest risk of CINV, requiring triple therapy.  
Intervention: NEPA 300 mg/0.50 mg given orally as a single dose.  
Comparator: Palonosetron 0.50 mg given orally as a single dose.  
Outcomes: The outcome of complete response (no emesis and no rescue medication) is appropriate for evaluating antiemetics.  
Setting: Conducted in 177 sites in 15 countries.  
Analysis:  
In female patients with predominately breast cancer, the combination of netupitant and palonosetron was more effective for the delayed phase than palonosetron alone in patients taking a MEC regimen. Acute phase results were also positive but need to be studied further.  

AC= Anthracycline-cyclophosphamide; CINV= chemotherapy-induced nausea and vomiting; ECOG=Eastern Cooperative Oncology Group; FAS= full analysis set; HEC=high emetogenic chemotherapy; MEC= moderately emetogenic chemotherapy; number needed to harm; NNT = number needed to treat; NR= not reported; PP = per protocol  

Author: K. Sentena, Pharm.D.  
Date: November 2015
References:


**Appendix 1: Current Status on Preferred Drug List**

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Appendix 2: Abstracts of Clinical Trials


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 1465 chemotherapy-naive 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 endpoint 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 endpoints 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.


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/m(2) 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% vs 41%; odds ratio [OR], 1.92; 95% CI, 1.23 to 3.00; P = .0042). Absence of major nausea (94% vs 88%; OR, 2.37; 95% CI, 1.09 to 5.15; P = .026) and emesis (78% vs 65%; OR, 1.99; 95% CI, 1.25 to 3.18; P = .0036) within 120 hours was increased by aprepitant. Mean total FLIE score (± standard deviation) was 114 ± 18 for aprepitant and 106 ± 26 for placebo (P < .001). CONCLUSION: The addition of aprepitant resulted in significantly less CINV and had a positive effect on quality of life.

Author: K. Sentena, Pharm.D. Date: November 2015

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.


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

Author: K. Sentena, Pharm.D. Date: November 2015
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.


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-naive 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 ≥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 thiordazine, 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:

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Appendix 5: Prior Authorization Criteria

## Antiemetics

**Goal(s):**
- Promote preferred drugs.
- Reserve costly antiemetics for appropriate indications.
- Restrict chronic use (>3 days per week).
- If chemotherapy is more frequent than once weekly. For multi-day chemotherapy regimens, approve a quantity sufficient for three days beyond the duration of chemotherapy.

**Length of Authorization:**
3 days to 6 months (criteria specific)

**Requires PA:**
- Non-preferred drugs

**Covered Alternatives:**
Preferred alternatives listed at www.orpdl.org

**Check the Reason for PA:**
- Non-Preferred drugs will be subject to PA criteria and quantity limits (Table 1) will deny on initiation.
- Preferred drugs will deny only when maximum dose exceeded.

### Table 1. Quantity Limits for Antiemetic Drugs

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<td>3 doses / 7 days</td>
</tr>
<tr>
<td>016576</td>
<td>Dolasetron</td>
<td>Anzemet</td>
<td>9 doses / 7 days</td>
</tr>
<tr>
<td>007611</td>
<td>Granisetron</td>
<td>Kytril Tablets</td>
<td>6 doses / 7 days (30 ml liquid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kytril solution</td>
<td>1 patch / 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sancuso transdermal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Netupitant/palonosetron</td>
<td>Akynzeo</td>
<td>1 dose / 7 days</td>
</tr>
<tr>
<td></td>
<td>Rolapitant</td>
<td>Varubi</td>
<td>1 dose / 7 days</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>Zofran</td>
<td>&gt; 4 days / 7 days</td>
</tr>
</tbody>
</table>

### Approval Criteria

1. What is the diagnosis being treated? Record ICD9 Code.
2. Is the drug requested preferred?
   Yes: Go to #4
   No: Go to #3.

3. Will the prescriber consider a change to the preferred product?
   Message:
   - Preferred products do not require PA for < 4 days/week.
   - Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.
   Yes: Inform provider of covered alternatives in class and dose limits. If dose > limits, continue to #4.
   No: Go to #4.

4. Is client currently diagnosed with cancer AND receiving multi-day chemotherapy or radiation therapy more frequently than every 7 days?
   Yes: Approve for 3 days past length of therapy. (Chemo regimen more frequently than weekly)
   No: Go to #5.

5. Is the request for aprepitant, dolasetron, granisetron, netupitant/palonosetron, rolapitant or ondansetron (>4 days) and the client is currently diagnosed with cancer and receiving chemotherapy or has had surgery within the last 5 days?
   Yes: Approve for quantity limits outlined in table 1.
   No: Go to #6

6. Does client have refractory nausea that would require hospitalization or ER visits?
   Yes: Go to #7.
   No: Go to #8.

7. Has client tried and failed two conventional antiemetics, listed below?
   Yes: Approve up to 6 months.
   No: Go to #8.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>Reglan</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Compazine</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Phenergan</td>
</tr>
<tr>
<td>Question</td>
<td>Yes:</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>8. Does client have contraindications to conventional antiemetics, e.g. allergy; or cannot tolerate?</td>
<td>Document reason and approve up to 6 months. (Contraindications to required alternative medications)</td>
</tr>
<tr>
<td>9. Is the client pregnant and the request is for doxylamine/pyridoxine (Diclegis)?</td>
<td>Approve for 15 days</td>
</tr>
<tr>
<td>10. RPH only</td>
<td></td>
</tr>
<tr>
<td>- All other indications need to be evaluated as to whether they are above the line or below the line.</td>
<td></td>
</tr>
<tr>
<td>• Above: Deny, (Medical Appropriateness)</td>
<td></td>
</tr>
<tr>
<td>• Below: Deny, (Not Covered by the OHP)</td>
<td></td>
</tr>
</tbody>
</table>

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