Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Class Literature Scan: Newer Antiemetics

Date of Review: September 2017

Date of Last Review: January 2016
Literature Search: 03/27/17 – 04/17/17

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- A search of the evidence on antiemetics identified three systematic reviews and meta-anlayses,[1–3] four guidelines,[4–7] two new formulations and one new indication.[8–10] There was insufficient evidence on subgroup populations and analyses related specifically to Medicaid patients. The evidence contributing to this review supports current antiemetic policy or lacks the quality of evidence required to prompt change to current preferred drug list (PDL) recommendations.
- A Cochrane review was performed on antiemetic use for the prevention and treatment of chemotherapy induced nausea and vomiting in children.[2] There was insufficient evidence to pool results of comparisons. Evidence was limited and firm conclusions were not identified. In a comparison of combination treatment with 5-hydroxytryptamine-3 receptor antagonists (5-HT3 RA) and dexamethasone compared to 5-HT3 RAs alone, more patients experienced no vomiting with combination therapy. A second comparison found rates of emesis were reduced with granisetron compared to ondansetron for control of vomiting in the acute phase (pooled relative risk [RR] 2.26; 95% CI, 2.04 to 2.51; ARR not available) but nausea comparisons and delayed phase results suggest similar efficacy.[2]
- A small number of trials with few patients found ondansetron to be as effective as metoclopramide in prevention of nausea symptoms and vomiting episodes in pregnant women with nausea and vomiting or hyperemesis gravidarum (low quality evidence).[1,3]
- Guidelines recommend a neurokinin 1 receptor antagonist (NK1 RA), a 5-HT3 RA and dexamethasone for the prevention of acute and delayed nausea and vomiting in patients receiving chemotherapy.[4,6] The American Society of Clinical Oncology (ASCO) guideline update recommends the NK1 RA netupitant and palonosetron (NEPA) as an option for a three-drug regimen in patients receiving highly emetogenic chemotherapy (HEC).[4] The recommendation was based on two phase three trials but was not graded. NEPA was previously reviewed and presented to the P and T committee. Conclusions are presented below.
- Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASSC/ESMO) guidelines on anticipatory nausea and vomiting in adults and children receiving chemotherapy remain unchanged from the 2011 update due to no new evidence.[5] Optimizing management of acute and delayed phase nausea and vomiting is recommended as the most effective preventative strategy for avoiding anticipatory manifestations.
- Updated guidance from MASSC/ESMO on prevention of nausea and vomiting in patients receiving chemotherapy, radiation, multiple-day chemotherapy, or high-dose chemotherapy and patients with advanced cancer, or breakthrough nausea or vomiting were published in 2016 and support the current policy recommendations for antiemetics.[6,7]

Author: Kathy Sentena, PharmD

- A new extended-release granisetron (ERG) formulation (Sustol®) was approved by the FDA to be used in combination with other antiemetics for the prevention of acute and delayed chemotherapy induced nausea and vomiting for patients receiving moderately emetogenic chemotherapy (MEC) and anthracycline and cyclophosphamide combination chemotherapy.[8] Approval was based on one trial which demonstrated ERG to be non-inferior to palonosetron.
- An extended-release formulation of doxylamine 20 mg and pyridoxine 20 mg (Bonjesta®) was approved for nausea and vomiting in pregnant women.[9] No new evidence was available for analysis. Approval was based off data demonstrating bioequivalence between two combination tablets of doxylamine 10 mg and pyridoxine 10 mg to the fixed dose combination of doxylamine 20 mg and pyridoxine 20 mg.
- Review of 2016 fourth quarter utilization data for the antiemetic class shows PDL adherence to be 98% for the preferred agent ondansetron.

Recommendations:
- Literature evaluated in this review supports the current preferred drug list (PDL) status of therapies in the antiemetic class.
- No further review or research is needed at this time. After evaluation of comparative drug costs in executive session, no PDL changes were recommended.

Previous 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. Key recommendations from clinical practice guidelines include up to 3 days of an antiemetic for patients beyond length of the chemotherapy regimen or radiation.
- 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).
- 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. 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. 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. 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%.
- There is insufficient data on the comparative effectiveness of the NK1 RA rolapitant (Varubi™). Currently, only prescribing information could be found.

Previous 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.

Fourth Quarter 2016 Utilization:

Fourth quarter (10/1/16 through 12/31/16) utilization data for the newer antiemetics for the Oregon Medicaid fee-for-service (FFS) population shows the preferred agent, ondansetron, resulted in the majority of utilization. Claims for non-preferred agents were for doxylamine/pyridoxine (Diclegis) and rolapitant (Varubi).

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan 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), the Cochrane Collaboration, 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 (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane: Antiemetics for the Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Childhood

A systematic review and meta-analysis evaluated pharmacotherapies used for anticipatory, acute and delayed nausea and vomiting in children (less than 18 years) who are receiving or about to receive chemotherapy.[2] Pharmacotherapies included were: 5-HT3 RAs, benzodiazepines, cannabinoids, corticosteroids, cyclizine, dopamine blockers, and levomepromazine (not available in the US). NK1 RAs and non-pharmacological therapy were not included. Thirty-four RCTs were available for analysis, 27 investigating the treatment of acute nausea and vomiting (1719 patients). Outcomes assessed included complete control of nausea (no nausea and no rescue medication) in the acute phase (first 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours of treatment with chemotherapy) and complete control of vomiting in both the acute and delayed phase. No trials assessed anticipatory nausea or vomiting. There was limited data beyond the first 24 hours of chemotherapy. Nausea outcomes were inconsistently reported and were not assessed via a validated measurement.

Pooled analysis of trial data was not possible for many of the trials due to the quality and quantity of trials identified. The effects of dexamethasone added to 5-HT3 RAs (ondansetron and granisetron) were studied in 2 trials.[2] The combination dexamethasone/5HT3 RA group completely controlled vomiting in more patients

than 5-HT3 RAs alone (RR 2.03; 95% CI, 1.35 to 3.04) (ARR not provided). Granisetron 20 mcg/kg was compared to granisetron 40 mcg/kg for complete control of vomiting and found to have similar efficacy (pooled RR 0.93; 95% CI, 0.80 to 1.07). No differences were found between granisetron 10 mcg/kg and 40 mcg/kg in controlling acute vomiting. Data from three trials suggest that granisetron was more effective than ondansetron for acute vomiting (pooled RR 2.26; 95% CI, 2.04 to 2.51); however complete control of acute nausea (pooled RR 1.05; 95% CI, 0.94 to 1.17), delayed nausea (pooled RR 1.13; 95% CI, 0.93 to 1.38) and delayed vomiting (pooled RR 1.13; 95% CI, 0.98 to 1.29) were similar between the two treatments.[2] Evidence was insufficient to make firm conclusions. Data on cannabinoids was conflicting and results were not able to be pooled.

Cochrane: Interventions for Treating Hyperemesis Gravidarum

The efficacy and safety of treatments for hyperemesis gravidarum in patients who were pregnant up to 20 weeks' gestation were included.[1] Studies of nausea and vomiting in pregnancy were excluded. Of the newer antiemetics, only 2 trials evaluated ondansetron were included in the review. Very low evidence based on one trial of 83 women found similar efficacy between metoclopramide and ondansetron. Severity of nausea and vomiting was similar between metoclopramide and ondansetron based on a 10-point visual analog scale (MD 1.70; 95% CI, -0.15 to 3.55).[1] Metoclopramide was associated with a higher incidence of drowsiness and dry mouth. A trial evaluating duration of hospital admission found no difference between ondansetron and promethazine based on very low quality evidence.

McParlin et al – Treatment for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy

In a systematic review, evidence for treatment of nausea and vomiting and hyperemesis gravidarum were reviewed.[3] Authors declared no conflict of interest and the analysis was funded by the National Institute for Health Research Technology Assessment Program. Seventy-eight trials were identified, 67 were RCTs. The American Heart Association (AHA) evidence grade and recommendation methodology was used to grade each assessment. Strength of the recommendation ranged from level A (high quality) to level C (expert opinion) and quality of evidence from class I (strong) to class III (harm). A meta-analysis was not possible due to heterogeneity and incomplete findings. A multitude of interventions were studied; however, for this analysis only results for newer antiemetics will be presented.

Five RCTs evaluated pyridoxine/doxylamine in the treatment of nausea and vomiting in pregnancy or hyperemesis gravidarum and determined the combination to be effective in women with moderate to severe symptoms as a second-line therapy (Level A, class IIa). In three trials (n=280) comparing pyridoxine/doxylamine to placebo or ondansetron, symptom improvement was demonstrated in both groups with higher rate of improvement in the pyridoxine/doxylamine group with a mean change in Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score of 4.8 versus 3. 9 (p=0.006). The PUQE measures symptoms on a scale of 0 (no symptoms) to 15 (worst possible symptoms). A small trial (n=60) in pregnant women found pyridoxine/doxylamine demonstrated reduced risk of recurrence of symptoms when used preventatively. Symptoms occurred in 15.4% of patients treated with pyridoxine/doxylamine compared to 39.1% in the group that was treated after symptoms presented (p<0.04; ARR 23.7%; NNT 4).[3] Seven RCTs with low or unclear risk of bias evaluated 5-HT3 RAs compared to placebo or active treatment. Authors concluded that 5-HT3 RAs were effective for all severity levels of nausea and vomiting (Level A, class IIa).

New Guidelines:

ASCO – Antiemetic Focused Guideline Update

A 2015 ASCO clinical practice guideline on the use of antiemetics was published to evaluate the combination of netupitant and palonosetron (NEPA) for prevention of acute and delayed nausea and vomiting due to chemotherapy.[4] ASCO guideline process is to grade the literature and make recommendations based on the strength of the evidence; however, the grading of trials included in the analysis was not provided.

ASCO recommends that patients who receive HEC (including anthracycline and cyclophosphamide) should be offered a three-drug antiemetic regimen.[4] A combination regimen of a NK1 RA, 5-HT3 RA and dexamethasone are recommended. An additional option is the combination of oral NEPA plus dexamethasone (recommendation grade not provided). Previous recommendations found in the 2011 update were unchanged:

- The preferred 5-HT3 RA for patients receiving MEC is palonosetron in addition to a corticosteroid.
- Antiemetic therapy should be based on the chemotherapy agent that has the highest emetic risk if the patient is receiving multiple chemotherapy agents.
- Patients receiving HEC should receive dexamethasone and a 5-HT3 RA.
- 5-HT3 RA and corticosteroids should be used for pediatric patients receiving MEC or HEC.
- HEC radiotherapy should be treated with a 5-HT3 RA before each fraction and a 5-day course of dexamethasone. The same recommendations apply for MEC radiotherapy, but the 5-day course of dexamethasone is optional.
- Patients receiving combination radiation therapy and chemotherapy should receive an antiemetic based on the emetogenicity of chemotherapy unless there is more risk of emesis with radiation.

2016 MASCC and ESMO Guidelines for Nausea and Vomiting Prevention in Patients Receiving Chemotherapy and Radiotherapy and in Advanced Cancer Patients

Updated MASCC/ESMO recommendations from the 2010 guideline were published on the most effective management of nausea and vomiting in patients undergoing treatment for malignancy with advanced cancer.[6] The level of evidence and the grading of the recommendations according to ESMO were based on adaptations of the grading methodology used by the Infectious Diseases Society of America (IDSA). IDSA grades the strength of the recommendation as the following: A (good evidence), B (moderate evidence) and C (poor evidence). The quality of the evidence is also graded: I (high quality from more than one randomized trials), II (evidence from more than one body of evidence that is not randomized or from a cohort or case-controlled study) or II (expert opinion evidence). The MASCC evaluates the evidence based on the levels of Scientific Confidence. The ranges were the following: high, moderate, low, very low and no confidence. Each recommendation received an assessment according to both the ESMO and MASCC. MASCC and ESMO were solely responsible for the funding the guidelines. Thirteen authors had conflicts of interest and six had none.

Treatment recommendations for prophylaxis of acute and delayed nausea and vomiting are presented in **Table 1**.[6] **Table 2** outlines the antiemetic treatment options for patients receiving radiation therapy. **Table 3** provides recommendations for antiemetic prophylaxis for children receiving chemotherapy. Lastly, the guidelines recommend prophylaxis with metoclopramide for prevention of emesis in patients with advanced cancer (MASCC high level of consensus and moderate level of confidence, ESMO level of evidence: III, ESMO grade of recommendation: C). Other prophylaxis options are: haloperidol, levomepromazine (not available in the US) or olanzapine. In patients with malignant bowel obstruction, octreotide is recommended with a conventional antiemetic. If relief is suboptimal, then the use of an anticholinergic anti-secretory agent and/or corticosteroids is recommended in combination with the other agents or as an alternative. There was no evidence to support the use of antiemetics for opioid-induced nausea and vomiting.

Table 1. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Patients Receiving Chemotherapy.[6]

Indication	Recommendation	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
Non-AC highly emetic chemotherapy	3 drug regimen: single doses of 5-HT3 RA, dexamethasone and an NK1 RA given before chemotherapy	High/ high	I/A

Non-AC highly emetic chemotherapy	Dexamethasone on days 2-4 in combination with the above	High/ moderate	I/B
Women with breast cancer receiving AC chemotherapy	3 drug regimen: single doses of 5-HT3 RA, dexamethasone and an NK1 RA given before chemotherapy	High/ high	I/A
Women with breast cancer receiving AC chemotherapy	Dexamethasone should be given on days 2-3 with the above except if fosaprepitant, netupitant or rolapitant were used on day 1	Moderate/ moderate	II/B
Olanzapine Use – prophylaxis of delayed nausea and in prevention of acute symptoms	Olanzapine may be appropriate, especially for nausea, with a 5-HT3 RA plus dexamethasone	Low/ low	II/B
Prevention of acute emesis in MEC	5-HT3 RA plus dexamethasone	Moderate/ moderate	II/B
Prevention of delayed emesis in patients receiving MEC with known potential for delayed emesis	Dexamethasone on days 2-3	Low/ moderate	III/C
Prevention of delayed emesis in patients receiving MEC	No routine prophylaxis	No confidence possible/ high	IV/D
Prevention of carboplatin-induced acute nausea and vomiting	NK1 RA, dexamethasone and 5-HT3 RA	Moderate/ moderate	II/B
Prevention of carboplatin-induced delayed nausea and vomiting	If fosaprepitant, netupitant or rolapitant were used on day 1 then no antiemetic prophylaxis is required. If aprepitant is given on day 1 then aprepitant should be given on days 2-3	Moderate/ moderate	II/B
Metastatic germ cell tumors receiving multiple-day cisplatin acute nausea and vomiting prevention	5-HT3 RA plus dexamethasone plus aprepitant	Moderate/ moderate	II/B
Metastatic germ cell tumors receiving multiple-day cisplatin delayed nausea and vomiting prevention	Dexamethasone is recommended	Moderate/ moderate	II/B
Prevention of nausea and vomiting with low or minimal emetogenic chemotherapy	A single regimen of dexamethasone or 5-HT3 RA or a dopamine RA (e.g., metoclopramide) may be considered	No confidence possible/ moderate	II/B
Prevention of nausea and vomiting with minimal emetogenic chemotherapy	No antiemetic should be routinely administered before chemotherapy if no history of nausea or vomiting	No confidence possible/ high	IV/D
Prevention of delayed nausea and vomiting with minimal emetogenic chemotherapy	No antiemetic should be routinely administered before chemotherapy if no history of nausea or vomiting	No confidence possible/ high	IV/D
Treatment of breakthrough nausea and vomiting	Use of an antiemetic with a different mechanism of action than that of the antiemetic used for prophylaxis Olanzapine 10 mg orally for 3 days is recommended	Moderate/ moderate	II/B
Anticipatory nausea and vomiting	Benzodiazepines are recommended	Moderate/moderate	II/A
Anticipatory nausea and vomiting	Behavioral therapies including: progressive muscle relaxation training, systematic desensitization and hypnosis	Moderate/moderate	II/B

High-dose chemotherapy for stem cell transplant	Combination of 5-HT3 RA with dexamethasone and aprepitant (124 mg on day 1 and 80 mg on days 2-4)	High/high	I/A

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, palonosetron); AC-anthracycline-cyclophosphamide; MEC – moderately emetogenic chemotherapy; NK1 RA – neurokinin 1 receptor antagonist (aprepitant, fosaprepitant, netupitant, rolapitant)

Table 2. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Patients Receiving Radiotherapy.[6]

Emetic Risk Level	Area of Treatment	Antiemetic Guideline	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High	Total body irradiation	Prophylaxis with a 5-HT3 RA and dexamethasone	High/high Moderate/high - for addition of dexamethasone	II/B IIIC – for addition of dexamethasone
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT3 RA and optional dexamethasone	High/high Moderate/high – for the addition of dexamethasone	II/A II/B - for the addition of dexamethasone
Low	Cranium	Prophylaxis or rescue with dexamethasone	Low/high	IV/D
Low	Head and neck, thorax region and pelvis	Prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist or a 5-HT3 RA	Low/high	IV/D
Minimal	Extremities, breast	Rescue with dexamethasone, a dopamine receptor antagonist or 5-HT3	Low/high	IV/D
Concomitant chemotherapy	Any area	Follow recommendations for antiemetic prophylaxis for chemotherapy regimen unless the RT regimen has a higher emetic risk and then treatment recommendation should be followed according to the highest risk	Low/high	IV/D

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, palonosetron); RT – radiation therapy

Table 3. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Children Receiving Chemotherapy.[6]

Indication	Recommendation	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High emetic risk chemotherapy	5-HT3 RA plus dexamethasone plus aprepitant	High/high	II/B
High emetic risk chemotherapy and patient is unable to receive dexamethasone	5-HT3 RA plus aprepitant	Moderate/high	II/B
High emetic risk chemotherapy and patient is unable to receive aprepitant	5-HT3 RA plus dexamethasone	Moderate/high	II/B
Medium emetic risk chemotherapy	5-HT3 RA plus dexamethasone	Moderate/high	II/B
Medium emetic risk chemotherapy and patient is unable to receive dexamethasone	5-HT3 RA plus aprepitant	Moderate/high	II/B
Low emetic risk chemotherapy	5-HT3 RA	Moderate/moderate	II/B
Minimal emetic risk chemotherapy	No antiemetic prophylaxis is recommended	Moderate/high	V/D

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, tropisetron, palonosetron)

MASCC/ESMO Anticipatory Nausea and Vomiting in Adults and Children Receiving Chemotherapy

In 2016, the MASCC/ESMO updated their 2011 recommendations on the treatment of patients with anticipatory nausea and vomiting who are receiving chemotherapy.[5] Evidence was graded as described in the MASCC/ESMO guideline above. An updated literature search was performed with the following inclusion criteria: full text primary studies; published in English; evaluated an intervention for the treatment of nausea and vomiting; the outcome of complete control was measured; and included at least 10 participants. No new literature was found meeting the inclusion criteria. Previous recommendations of optimizing acute and delayed phase nausea and vomiting control for prevention of anticipatory nausea and vomiting were reiterated (MASCC moderate confidence and high consensus and ESMO level of evidence III and grade A). Behavioral therapies and benzodiazepines can also be considered for treatment.

MASCC/ESMO Recommendations for Prevention of Nausea and Vomiting Following Multi-Day Chemotherapy, High-dose Chemotherapy and Breakthrough Nausea and Vomiting

Multiple day chemotherapy regimens, high-dose chemotherapy and breakthrough nausea and vomiting are conditions that require specialized management for the prevention of nausea and vomiting.[7] In the recent MASCC/ESMO recommendations, updated evidence on antiemetic treatment options for patients with these conditions included two new RCTs. Guideline development utilized the IDSA and Scientific Confidence methodology described above. Changes from the previous recommendations included olanzapine for breakthrough pain and the use of aprepitant for multiple-day regimens and high-dose regimens. Recommendations for prevention of nausea and vomiting are as follows:

- In the acute phase receiving multiple-day cisplatin chemotherapy
    - 5-HT3 RA, dexamethasone and aprepitant (moderate confidence/moderate consensus and ESMO level II/B)[7]
- In the delayed phase receiving multiple-day cisplatin chemotherapy
    - Dexamethasone and aprepitant (moderate confidence/moderate consensus and ESMO level II/B)[7]
- Breakthrough

- Olanzapine 10 mg daily for three days (moderate confidence/moderate consensus and ESMO level II/B)[7]

- High-dose chemotherapy for stem cell transplant
  - 5-HT3 RA, dexamethasone and aprepitant (high confidence/high consensus and ESMO level I/A)[7]

New Formulations:

A new extended-release granisetron (ERG) injection (Sustol®) was approved in 2016 for the use in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting with initial and repeat courses of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide combination chemotherapy regimens.[8] ERG injection should be given as a 10 mg subcutaneous (SQ) dose at least 30 minutes before the start of emetogenic chemotherapy on Day 1. ERG injection should not be given more than once every 7 days and for not more than 6 months in patients receiving successive emetogenic chemotherapy cycles.

ERG 10 mg SQ was approved based on one clinical trial comparison to palonosetron 0.25 mg IV.[8] The trial was a multi-center, double-blind, parallel group study in patients with cancer undergoing treatment with MEC or anthracycline plus cyclophosphamide combination chemotherapy. A single dose of each agent, in combination with IV dexamethasone 8 mg or 20 mg, was given 30 minutes prior to chemotherapy on Day 1. The study population (n=733) was 63% Caucasian and 79% female with a mean age of 57 years. MEC was given to 55% of patients and 45% received combination therapy with anthracycline and cyclophosphamide. The primary endpoint was the percent of patients obtaining a complete response (defined as no emetic episodes and no rescue medication use) in the acute phase (within 24 hours) and the delayed phase (>24 to 120 hours) following chemotherapy. A complete response was demonstrated in 166 (83%) of patients receiving ERG and in 183 (89%) of patients receiving palonosetron in the acute phase receiving MEC.[8] In the delayed phase, ERG was associated with a complete response in 137 (69%) of patients and in 144 (70%) in palonosetron treated patients.[8] In patients receiving anthracycline and cyclophosphamide, there was a complete response rate in the acute phase in 120 (70%) of patients receiving ERG and 99 (64%) of patients receiving palonosetron. ERG was associated with 85 (50%) of patients treated with ERG obtaining a complete response compared to 74 (47%) in the palonosetron group during the delayed phase. ERG was shown to be non-inferior, but not superior, to palonosetron.

The most common adverse reactions are injection site reactions, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, asthenia and gastrointestinal reflux. Hypersensitivity reactions have occurred up to 7 days or longer after an ERG injection.

Additional RCTs are presented below and abstracts are available in **Appendix 3**.

Table 4. Description of Randomized Comparative Clinical Trials for Extended-Release Granisetron.

Study	Comparison	Population	Primary Outcome	Results
Raftopoulos, et al[11] RCT, DB, MC, Phase 3, non-inferiority	ERG 5 mg SQ or ERG 10 mg SQ vs. Palonosetron 0.25mg IV One dose 30-60 min. prior to chemotherapy Both treatments were given with IV dexamethasone HEC regimens were also given oral dexamethasone 8 mg twice daily on days 2-4	Adults with confirmed malignancy and scheduled to receive MEC or HEC during first cycle N=1,341	The percentage of patients obtaining a complete response in the acute and delayed phase (no emetic episodes and no use of rescue medication during acute and delayed phase)	<u>MEC Acute Phase</u> ERG 5 mg: 160 (74.8%) ERG 10 mg: 163 (76.9% Palonosetron: 156 (75.0%) ERG 5 mg vs. Palonosetron: P = 1.0 ERG 10 mg vs. Palonosetron: P = 0.73 <u>MEC Delayed Phase</u> ERG 5 mg: 110 (51.4%) ERG 10 mg: 124 (58.5%) Palonosetron: 119 (57.20%) ERG 5 mg vs. Palonosetron: P = 0.24 ERG 10 mg vs. Palonosetron: P = 0.84 <u>HEC Acute Phase</u> ERG 5 mg: 178 (77.7%) ERG 10 mg: 195 (81.3%) Palonosetron: 192 (80.7%) ERG 5 mg vs. Palonosetron: P = 0.49 ERG 10 mg vs. Palonosetron: P = 0.91 <u>HEC Delayed Phase</u> ERG 5 mg: 143 (62.4%) ERG 10 mg: 161 (67.1%) Palonosetron: 153 (64.3%) ERG 5 mg vs. Palonosetron: P = 0.70 ERG 10 mg vs. Palonosetron: P = 0.56 • CI not provided for results
Schnadig, et al[12] RCT, DB, DD, PG, MC, Phase 3	ERG 10 mg SQ vs. Ondansetron 0.15 mg/kg IV Both treatments were given with dexamethasone 12 mg IV and fosaprepitant 150 mg IV. Regimens were also given oral	Adults with confirmed malignancy scheduled to receive highly emetogenic chemotherapy receiving their first cycle	Delayed phase (24-120 hours) complete response (no emesis or rescue medication)	ERG 10 mg: 291 (64.7%) Ondansetron: 256 (56.6%) ARR 8.0% (95% CI, 1.7 to 14.4) P = 0.014

	dexamethasone 8 mg once daily on day 2 and twice daily on days 3-4.	N = 450		
Boccia, et al[13] RCT, MC, DB, PC, PG, Phase 3	<u>Cycle 1</u> ERG 5 mg SC or ERG 10 mg SC vs. Palonosetron 0.25 mg IV <u>Cycle 2-4</u> ERG 5 mg SC vs. ERG 10 mg SC Both treatments were given with IV dexamethasone	Adults with confirmed malignancy receiving MEC or HEC N = 1,395	Complete response (no emetic episodes, no rescue medication) of ERG 10 mg during acute (0-24 hours) and delayed (>24-120 hours) phases during chemotherapy cycles 2-4	<u>Complete Response HEC Acute Phase</u> ERG 10 mg cycle 1: 81.3% ERG 10 mg cycle 4: 87.8% Palonosetron cycle 1: 75% <u>Complete Response HEC Delayed Phase</u> ERG 10 mg cycle 1: 67.1% ERG 10 mg cycle 4: 83.1% Paonosetron cycle 1: 81% * Results for palonosetron cycle 4 were not provided.

Abbreviations: ARR = actual risk reduction; DB = double-blind; DD = double-dummy; ERG = extended-release granisetron; HEC = highly emetogenic chemotherapy; IV = intravenous; MC = multi-center; MEC = moderately emetogenic chemotherapy; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; SQ = subcutaneous.

<u>Doxylamine/Pyridoxine (Bonjesta)</u>

A new extended-release, fixed dose formulation of the currently available doxylamine/pyridoxine was approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.[9] The combination product is 20 mg doxylamine and 20 mg pyridoxine to be given as one tablet at bedtime on Day 1. If symptoms are not adequately controlled on Day 2, then the dose can be increased to one tablet in the morning and one tablet at bedtime. The maximum dosage is 2 tablets a day.

The extended-release doxylamine/pyridoxine formulation was not studied in clinical trials. The approval was based on a clinical trial of doxylamine 10 mg/pyridoxine 10 mg (Diclegis) formulation that has been previously reviewed.[9] A pharmacokinetic crossover trial of 48 women found extended-release doxylamine 20 mg/pyridoxine 20mg to be bioequivalent to two combination tablets of 10 mg doxylamine and 10 mg pyridoxine. A second multi-dose, crossover trial found bioequivalence of one ER doxylamine 20 mg/pyridoxine 20 mg tablet given twice daily to one tablet of doxylamine 10 mg/pyridoxine 10 mg given three times daily.

<u>Aprepitant Use in Pediatrics</u>

In 2015, aprepitant (Emend) was approved for pediatric use (ages 12 to 17 years and for patients less than 12 years who weight at least 30 kg) for the prevention of chemotherapy-induced acute and delayed nausea and vomiting in combination with other antiemetic agents for patients receiving initial and repeat MEC or

HEC (including cisplatin) regimens.[10] The dose for pediatric patients is the same as for adults, 125 mg aprepitant on day 1 and 80 mg on days 2 and 3. The study used for the pediatric indication is presented below.

Table 5. Description of Randomized Comparative Clinical Trials for Aprepitant.

Study	Comparison	Population	Primary Outcome	Results
Kang, et al[14] RCT, MC, Phase 3, DB	Aprepitant* vs. Placebo† * Aprepitant 125 mg orally for 12-17 years; 3.0 mg/kg (maximum 125 mg) orally for ages 6 mo. to <12 years and ondansetron on day 1. On day 2 and 3, aprepitant 80 mg for ages 12-17 years and 2.0 mg/kg (max 80 mg) for ages 6 months to <12 years. Ondansetron was given on day 1 according to manufacturer recommendations. † Oral placebo and ondansetron were given on day 1. Placebo only was given on days 2 and 3. Ondansetron dosing was based on manufacturer's recommendation. *† Dexamethasone IV was allowed for both groups	Patients 6 months to 17 years with documented malignancy receiving MEC or HEC N = 307	The proportion of patients who obtained a complete response (no vomiting, retching or use of rescue medications) in the delayed phase (25-120 hours post chemotherapy)	<u>Delayed phase</u> Aprepitant: 77 (51%) Placebo: 39 (26%) ARR: 25%; P < 0.0001

Abbreviations: ARR = actual risk reduction; DB = double-blind; HEC = highly emetogenic chemotherapy; IV = intravenous; MC = multi-center; MEC = moderately emetogenic chemotherapy; PC = placebo controlled; RCT = randomized clinical trial.

New FDA Safety Alerts:
No safety alerts identified.

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Appendix 1: Current 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
ORAL	TABLET	BONJESTA	DOXYLAMINE/PYRIDOXINE	N
INTRAVEN	VIAL	ALOXI	PALONOSETRON	
SUBCUTA	VIAL	SUSTOL	GRANISETRON	N

Appendix 2: New Comparative Clinical Trials

A total of 151 citations were manually reviewed from the initial literature search. After further review, 149 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining two trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Navari, et al[15] RCT, DB, Phase 3	Olanzapine 10 mg* vs. Placebo* * Given on days 1-4 Both groups received dexamethasone, aprepitant or fosaprepitant and a 5-hydroxy-tryptamine type 3-recetptor antagonist	Adult patients with malignant disease naïve to chemotherapy receiving cisplatin or cyclophosphamide-doxarubicin N=380	Nausea prevention (defined as zero on a visual analog scale for nausea) during the overall assessment (0-120 hours), the early assessment period (0-24 hours) and the later assessment period (25-120 hours)	<u>No nausea 0-24 hours</u> Olanzapine: 135 (74%) Placebo: 82 (45%) ARR: 29%; P = 0.002 <u>No nausea 25-120 hours</u> Olanzapine: 75 (42%) Placebo: 45 (25%) ARR: 17%; P = 0.002 <u>No nausea 0-120 hours</u> Olanzapine: 66 (37%) Placebo: 39 (22%) ARR: 15%; P = 0.002
Kovács, et al [16] MC, DB, DD, RCT, Phase 3	IV Palonosetron 10 mcg/kg* or IV Palonosetron 20 mcg/kg* vs. IV Ondansetron 150 mcg/kg given as 3 doses 4 hours apart on day 1 * Given up to 4 cycles on day 1	Pediatric patients (0-17 years) scheduled to receive MEC or HEC for treatment of malignant disease N=502	Complete response (no vomiting, retching or rescue drug treatment) during the acute phase (0-24 hours post-chemotherapy) during the first cycle of chemotherapy	<u>Complete Response</u> Palonosetron 10 mcg/kg: 90 (54%) Palonosetron 20 mcg/kg: 98 (59%) Ondansetron: 95 (59%) <u>Palonosetron 20 mcg/kg vs. Ondansetron</u> WSD 0.36% (97.5% CI, -11.7 to 12.4) P = 0.0022 (non-inferiority achieved) <u>Palonosetron 10 mcg/kg vs. Ondansetron</u> WSD -4.41% (97.5% CI, -16.4 to 7.6) P = NS

Abbreviations: ARR = absolute risk reduction; DB = double-blind; DD=double-dummy; IV = intravenous; MC = multi-center; RCT = randomized clinical trial; WSD = weighted sum of the difference

Appendix 3: Abstracts of Comparative Clinical Trials

Randomized phase III trial of APF530 versus palonosetron in the prevention of chemotherapy-induced nausea and vomiting in a subset of patients with breast cancer receiving moderately or highly emetogenic chemotherapy

Boccia R, Cooper W, Boyle E

Background

APF530 provides controlled, sustained-release granisetron for preventing acute (0–24 h) and delayed (24–120 h) chemotherapy-induced nausea and vomiting (CINV). In a phase III trial, APF530 was noninferior to palonosetron in preventing acute CINV following single-dose moderately (MEC) or highly emetogenic chemotherapy (HEC) and delayed CINV in MEC (MEC and HEC defined by Hesketh criteria). This exploratory subanalysis was conducted in the breast cancer subpopulation.

Methods

Patients were randomized to subcutaneous APF530 250 or 500 mg (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg during cycle 1. Palonosetron patients were randomized to APF530 for cycles 2 to 4. The primary efficacy end point was complete response (CR, no emesis or rescue medication) in cycle 1.

Results

Among breast cancer patients (*n* = 423 MEC, *n* = 185 HEC), > 70 % received anthracycline-containing regimens in each emetogenicity subgroup. There were no significant between-group differences in CRs in cycle 1 for acute (APF530 250 mg: MEC 71 %, HEC 77 %; 500 mg: MEC 73 %, HEC 73 %; palonosetron: MEC 68 %, HEC 66 %) and delayed (APF530 250 mg: MEC 46 %, HEC 58 %; 500 mg: MEC 48 %, HEC 63 %; palonosetron: MEC 52 %, HEC 52 %) CINV. There were no significant differences in within-cycle CRs between APF530 doses for acute and delayed CINV in MEC or HEC in cycles 2 to 4; CRs trended higher in later cycles, with no notable differences in adverse events between breast cancer and overall populations.

Conclusions

APF530 effectively prevented acute and delayed CINV over 4 chemotherapy cycles in breast cancer patients receiving MEC or HEC.

Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial

Raftopoulos H, Cooper W, O'Boyle, et al

Purpose

Subcutaneous APF530 provides controlled sustained release of granisetron to prevent acute (0–24 h) and delayed (24–120 h) chemotherapy-induced nausea and vomiting (CINV). This randomized, double-blind phase 3 trial compared APF530 and palonosetron in preventing acute and delayed CINV after moderately (MEC) or highly emetogenic chemotherapy (HEC).

Methods

Patients receiving single-day MEC or HEC received single-dose APF530 250 or 500 mg subcutaneously (SC) (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg. Primary objectives were to establish APF530 noninferiority to palonosetron for preventing acute CINV following MEC or HEC and delayed CINV following MEC and to determine APF530 superiority to palonosetron for preventing delayed CINV following HEC. The primary efficacy end point was complete response (CR [using CI difference for APF530 − palonosetron]). A lower confidence bound greater than −15 % indicated noninferiority.

Results
In the modified intent-to-treat population (MEC = 634; HEC = 707), both APF530 doses were noninferior to palonosetron in preventing acute CINV after MEC (CRs 74.8 % [−9.8, 9.3] and 76.9 % [−7.5, 11.4], respectively, vs. 75.0 % palonosetron) and after HEC (CRs 77.7 % [−11.5, 5.5] and 81.3 % [-7.7, 8.7], respectively, vs. 80.7 % palonosetron). APF530 500 mg was noninferior to palonosetron in preventing delayed CINV after MEC (CR 58.5 % [−9.5, 12.1] vs. 57.2 % palonosetron) but not superior in preventing delayed CINV after HEC. Adverse events were generally mild and unrelated to treatment, the most common (excluding injection-site reactions) being constipation.
Conclusions
A single subcutaneous APF530 injection offers a convenient alternative to palonosetron for preventing acute and delayed CINV after MEC or HEC.

APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy
Schnadig I, Agajanian R, Dakhil C, et al

AIM
APF530, extended-release granisetron, provides sustained release for ≥5 days for acute- and delayed-phase chemotherapy-induced nausea and vomiting (CINV). We compared efficacy and safety of APF530 versus ondansetron for delayed CINV after highly emetogenic chemotherapy (HEC), following a guideline-recommended three-drug regimen.
METHODS
HEC patients received APF530 500 mg subcutaneously or ondansetron 0.15 mg/kg intravenously, with dexamethasone and fosaprepitant. Primary end point was delayed-phase complete response (no emesis or rescue medication).
RESULTS
A higher percentage of APF530 versus ondansetron patients had delayed-phase complete response (p = 0.014). APF530 was generally well tolerated; treatment-emergent adverse event incidence was similar across arms, mostly mild-to-moderate injection-site reactions.
CONCLUSION
APF530 versus the standard three-drug regimen provided superior control of delayed-phase CINV following HEC.

Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial.
Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM.

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 paediatric 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, multicentre, 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. Randomisation 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 paediatric 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 ($p<0{\cdot}0001$). 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), anaemia (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 paediatric patients being treated with moderately or highly emetogenic chemotherapy.

FUNDING:

Merck & Co., Inc.

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting.

Navari RM, Qin R, Ruddy KJ, et al

BACKGROUND:

We examined the efficacy of olanzapine for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy.

METHODS:

In a randomized, double-blind, phase 3 trial, we compared olanzapine with placebo, in combination with dexamethasone, aprepitant or fosaprepitant, and a 5-hydroxytryptamine type 3-receptor antagonist, in patients with no previous chemotherapy who were receiving cisplatin (≥70 mg per square meter of body-surface area) or cyclophosphamide-doxorubicin. The doses of the three concomitant drugs administered before and after chemotherapy were similar in the two groups. The two groups received either 10 mg of olanzapine orally or matching placebo daily on days 1 through 4. Nausea prevention was the primary end point; a complete response (no emesis and no use of rescue medication) was a secondary end point.

RESULTS:

In the analysis, we included 380 patients who could be evaluated (192 assigned to olanzapine, and 188 to placebo). The proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine than with placebo in the first 24 hours after chemotherapy (74% vs. 45%, P=0.002), the period from 25 to 120 hours after chemotherapy (42% vs. 25%, P=0.002), and the overall 120-hour period (37% vs. 22%, P=0.002). The complete-response rate was also significantly increased with olanzapine during the three periods: 86% versus 65% (P<0.001), 67% versus 52% (P=0.007), and 64% versus 41% (P<0.001), respectively. Although there were no grade 5 toxic effects, some patients receiving olanzapine had increased sedation (severe in 5%) on day 2.

CONCLUSIONS:
Olanzapine, as compared with placebo, significantly improved nausea prevention, as well as the complete-response rate, among previously untreated patients who were receiving highly emetogenic chemotherapy. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT02116530.).

Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study.
Kovács G, Wachtel AE, Basharova EV, Spinelli T, Nicolas P, Kabickova E.
BACKGROUND:
Palonosetron has shown efficacy in the prevention of chemotherapy-induced nausea and vomiting in adults undergoing moderately or highly emetogenic chemotherapy. We assessed the efficacy and safety of palonosetron versus ondansetron in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients.
METHODS:
In this multicentre, multinational, double-blind, double-dummy, phase 3 study, paediatric patients aged between 0 and younger than 17 years, who were naive or non-naive to chemotherapy, and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease were randomised centrally (1:1:1) to receive up to four cycles of 10 μg/kg or 20 μg/kg palonosetron on day 1, or three 150 μg/kg doses of ondansetron on day 1, scheduled 4 h apart, according to a static central permuted block randomisation scheme by an interactive web response system. Randomisation was stratified according to age and emetogenicity. Treatment allocation was masked to project team members involved in data collection and analysis, and members of the investigator's team. The primary endpoint was complete response (no vomiting, retching, or use of rescue drugs) during the acute phase (0-24 h post-chemotherapy) of the first on-study chemotherapy cycle, as assessed in the population of randomly assigned patients who received moderately or highly emetogenic chemotherapy and an active study drug. The primary efficacy objective was to show the non-inferiority of palonosetron versus ondansetron during the acute phase (0-24 h post-chemotherapy) of the first on-study chemotherapy cycle through comparison of the difference in the proportions of patients who achieved a complete response with palonosetron (πT) minus ondansetron (πR) versus a preset non-inferiority margin (δ -15%). To be considered as non-inferior to ondansetron, for at least one of the doses of palonosetron, the lower limit of the 97·5% CI for the weighted sum of the differences in complete response rates had to be superior to -15%. Safety was assessed, according to treatment received. This study is registered with ClinicalTrials.gov, number NCT01442376, and has been completed.
FINDINGS:
Between Sept 12, 2011, and Oct 26, 2012, we randomly assigned 502 patients; 169 were assigned to receive 10 μg/kg palonosetron, 169 to receive 20 μg/kg palonosetron, and 164 to receive 3 × 150 μg/kg ondansetron, of whom 166, 165, and 162, respectively, were included in the efficacy analysis. In the acute phase, complete responses were recorded in 90 (54%) patients in the 10 μg/kg palonosetron group, 98 (59%) in the 20 μg/kg palonosetron group, and 95 (59%) in the ondansetron group. Non-inferiority versus ondansetron was shown for 20 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates 0·36% [97·5% CI -11·7 to 12·4]; p=0·0022). Non-inferiority versus ondansetron was not shown for 10 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates -4·41% [97·5% CI -16·4 to 7·6]). In the first on-study treatment cycle, treatment-emergent adverse events were reported in 134 (80%) of 167 patients who received 10 μg/kg palonosetron, 113 (69%) of 163 who received 20 μg/kg palonosetron, and 134 (82%) of 164 who received ondansetron. The most common drug-related treatment-emergent adverse events were nervous system disorders, mainly headache, which occurred in three (2%) patients who received 10 μg/kg palonosetron, one (<1%) patient who received 20 μg/kg palonosetron, and two (1%) patients who received ondansetron. The incidence of serious adverse events in the first on-study treatment cycle was lower in the 20 μg/kg palonosetron group (43 [26%]) than in the 10 μg/kg palonosetron group (52 [31%]) and the ondansetron group (55 [34%]).

INTERPRETATION:
Non-inferiority was shown for 20 µg/kg palonosetron during the acute phase of the first on-study chemotherapy cycle. 20 µg/kg palonosetron is now indicated by the European Medicines Agency and the US Food and Drug Administration for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients aged 1 month to younger than 17 years.
FUNDING:
Helsinn Healthcare.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to March Week 5 2017
Search Strategy:

#	Searches	Results
1	rolapitant.mp.	24
2	(netupitant and palonosetron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	34
3	ondansetron.mp. or Ondansetron/	2880
4	fosaprepitant.mp.	58
5	aprepitant.mp.	634
6	dolasetron.mp.	251
7	granisetron.mp. or Granisetron/	1093
8	(doxylamine and pyridoxine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	83
9	palonosetron.mp.	375
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	4474
11	limit 10 to (english language and humans and yr="2015 -Current")	296
12	limit 11 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	151

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs will be subject to PA criteria

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Will the prescriber consider a change to the preferred product? Message: • Preferred products do not require a PA. • 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.	**No:** Go to #3
3. Is the request for doxylamine/pyridoxine (Diclegis®) or (Bonjesta) for pregnancy-related nausea or vomiting?	**Yes:** Go to #4	**No:** Go to #5

4. Has the patient failed a trial of pyridoxine? Message: • Preferred vitamin B products do not require a PA. • 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.
5. Is the request for dronabinol (Marinol®)?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have anorexia associated with HIV/AIDS?	**Yes:** Approve for up to 6 months*	**No:** Go to #7
7. Does the patient have a cancer diagnosis and receiving chemotherapy or radiation?	**Yes:** Approve for up to 6 months	**No:** Go to #8
8. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	**Yes:** Approve for up to 6 months*	**No:** Go to #9
9. Has the patient tried and failed, or have contraindications, to at least 2 preferred antiemetics?	**Yes:** Approve for up to 6 months*	**No:** Pass to RPh. Deny; medical appropriateness. Must trial at least 2 preferred antiemetics.
* If the request is for dronabinol (Marinol®) do not exceed 3 doses/day for 2.5 mg and 5 mg strengths and 2 doses/day for the 10 mg strength.		

P&T / DUR Review: *7/17 (KS); 1/17 (DM) 1/16; 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*