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Drug Class Literature Scan: Newer Antiemetics

Date of Review: December 2020

Date of Last Review: September 2017
Literature Search: 07/01/17 – 10/09/20

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

Conclusions:

- There is one guideline, 2 systematic reviews, 2 new indications, 2 new formulations and 2 safety alerts providing evidence for this review. The evidence contributing to this review supports current antiemetic policy or lacks the quality of evidence to institute changes to the current preferred drug list (PDL).
- The National Institute for Health and Care Excellence (NICE) found evidence that doxylamine/pyridoxine was effective for improving Pregnancy Unique Quantification of Emesis (PUQE) scores. NICE recommends the use of doxylamine/pyridoxine for use in patients who prefer a licensed product for use in pregnancy.[1]
- A 2020 report by the Canadian Agency for Drugs and Technology in Health (CADTH) found ondansetron, when studied in pediatric patients with mild to moderate dehydration due to gastroenteritis, to decrease the need for intravenous (IV) rehydration and reduced the incidence of vomiting compared to placebo.[2]
- Updated 2020 National Comprehensive Cancer Network (NCCN) guidelines for antiemesis in cancer supports current policy.[1]

New Products/Formulations

- BARHEMSYS (amisulpride) is a is a dopamine-2 antagonist approved for the prevention and treatment of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class in adult patients. A complete response was seen in patients when treated with amisulpride for prophylaxis (number needed to treat [NNT] 8-9) and for treatment (NNT 8-10), both used as a single dose treatment within 24 hours of surgical procedure. Amisulpride offers a treatment option for patients not responding, or who cannot tolerate, current standard of care therapies for PONV (e.g., serotonin [5-HT3] receptor antagonists [RAs]).[3]
- CINVANTI (aprepitant) is a new formulation of injectable aprepitant 130 mg that was approved in October of 2019.[4] Aprepitant is approved as preventative therapy for acute and delayed nausea and vomiting associated with initial and repeat courses of medium emetogenic chemotherapy (MEC) and high emetogenic chemotherapy (HEC) regimens.
- EMEND (fosaprepitant) was approved for the use in pediatric patients 6 months of age and older for prevention of chemotherapy-induced nausea and vomiting (CINV).[5]
- Palonosetron – An expanded indication for palonosetron was approved in 2018 for patients 1 month to less than 17 years of age for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.[6]

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Recommendations:

- There is no new clinical evidence to warrant changes to the preferred drug list (PDL).
- After evaluation of costs in executive session, no PDL changes were made.

Summary of Prior Reviews and Current Policy

- A literature review of the clinical efficacy and safety of the antiemetic class in September of 2017 resulted in no changes to the PDL and after executive session there were also no changes to the PDL.
- Evidence recommends the use of the newer antiemetics (5-HT3 RAs, neurokinin 1 receptor antagonists [NK1 RAs]), in addition to drugs from other classes (e.g., olanzapine, dexamethasone, and benzodiazepines) for chemotherapy-induced and radiation-induced nausea and vomiting.
- The 5-HT3 RAs have been shown to have similar efficacy when studied at recommended doses and dosing intervals for chemotherapy induced nausea/vomiting.
- There is no evidence to suggest clinically significant differences between the newer antiemetics used for PONV.

- Current policy has ondansetron tablets, rapid tablets and solution as preferred therapies on the Oregon Health Plan (OHP) fee-for-service (FFS) PDL. Almost all claims are for preferred products (98%) and overall quarterly costs for the class are not substantial. Non-preferred products are subject to clinical PA criteria (**Appendix 5**).

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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.

New Systematic Reviews:

<u>NICE – Doxylamine/Pyridoxine for Treating Nausea and Vomiting of Pregnancy</u>

An evidence review for the use of doxylamine 10 mg/pyridoxine 10 mg in pregnant women with nausea and vomiting was conducted by NICE in 2019.[7] A literature search retrieved 2 randomized controlled trials available for analysis. There was evidence of improvement in symptoms of nausea and vomiting as demonstrated by the PUQE. The PUQE is a questionnaire consisting of 3 questions with scores ranging from 3-15. Higher scores indicate more severe nausea/vomiting, but no minimal clinically important difference has been reported.[7] Patients in the doxylamine/pyridoxine group demonstrated a reduction of -

4.8 in PUQE score compared to -3.9 for placebo (p=0.006).[7] A second study originally done in 1975, and published in 2017, substantiated results of the more recent study.

Recommendations from NICE, via the Royal College of Obstetricians and Gynecologists (RCOG), for the treatment of pregnancy related nausea and vomiting are as follows:

- First line: Antihistamines and phenothiazines
- Second line: metoclopramide, domperidone (not available in the United States [US]) or ondansetron
- Third line: corticosteroids

RCOG recommendations precede the approval of doxylamine/pyridoxine, and it can be recommended for patients who prefer a licensed antiemetic product for use in pregnancy.[7] Older therapies are not specifically approved for use in pregnancy but are the clinical standard in managing nausea and vomiting in this population.

There is only limited evidence on the topic, with short study periods (15 days) and use of a subjective, patient-reported outcome measure (e.g., PUQE). There are no active treatment comparison trials.

CADTH – Ondansetron and Oral Rehydration Therapy in Pediatric Patients with Dehydration: A Review of Clinical Effectiveness

A 2020 CADTH rapid response report evaluated the evidence for the efficacy of ondansetron, alone or in combination with oral rehydration, compared to oral rehydration alone in pediatric patients at risk of mild to moderate dehydration.[2] A literature search ranging from January 2015 to January 2020 identified 6 trials that met criteria for inclusion; 5 randomized clinical trials and 1 non-randomized retrospective comparative cohort study. All studies were conducted at sites other than the United States (US) with the exception of the non-randomized study.

Low strength of evidence found ondansetron to decrease the need for IV rehydration and reduce the incidence of vomiting compared to placebo, in pediatric patients with mild to moderate dehydration due to gastroenteritis (meta-analysis was not performed).[2] One trial found that ondansetron was not superior to placebo for reduction in vomiting. Non-randomized trial findings showed ondansetron to have no effect on emergency department readmissions within 72 hours, compared to no treatment.

After review, 14 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[8–21]

New Guidelines:

High Quality Guidelines:

NCCN – Anitemesis

The NCCN is a high-quality guideline which updates recommendations for antiemetic use in oncology on an annual basis.[1] Guidance recommendations are based on a NCCN categories of evidence and consensus (**Table 1**). All recommendations in the guideline are considered category 2A unless specifically noted otherwise.

Table 1. NCCN Categories of Evidence and Consensus[1]

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Chemotherapy related nausea/vomiting is referred to as CINV. Antiemetic therapies are categorized as: acute, delayed, anticipatory, breakthrough or refractory. The emetogenic potential of the chemotherapy or radiation regimen dictates the appropriate antiemetic therapy. Risk categories are as follows: high, moderate, low and minimal.[1] It is recommended that antiemetic therapies be initiated before treatment with anticancer therapies. Evidence demonstrates that antiemetics are equally effective and individual antiemetic selection should be based on drug-drug interactions, patient-specific factors and individual experience. Selection of antiemetic regimen should always be based on the drug with the highest emetic risk. Antiemetic treatment recommendations for parenteral anticancer therapies are provided in **Tables 2, 3 and 4**.[1] Parenteral anticancer therapies with minimal emetic potential require no routine prophylaxis.

Table 2. NCCN Recommendations for Acute and Delayed Emesis Prevention for High Emetic Risk Parenteral Anticancer Agents*†[1]

Day 1 (Select option A, B or C)	Days 2, 3, 4
Treatment option A (preferred) use the following combination: • Olanzapine orally once • NK1 RA once (PO or IV) • 5-HT3 RA once (PO, SQ or IV) • Dexamethasone once (PO or IV)	Treatment option A: • Olanzapine orally on days 2, 3 and 4 • Aprepitant 80 mg orally on days 2, 3 (if aprepitant orally was used on day 1) • Dexamethasone daily on days 2, 3, 4 (PO/IV)
Treatment option B, use the following combination: • Olanzapine orally once • Palonosetron once (IV) • Dexamethasone once (PO/IV)	Treatment option B: • Olanzapine orally daily on days 2, 3, 4
Treatment option C, use the following combination: • NK1 RA once (PO or IV) • 5-HT3 RA once (PO, SQ or IV) • Dexamethasone once (PO/IV)	Treatment option C: • Aprepitant 80 mg orally on days 2, 3 (if aprepitant PO was used on day 1) • Dexamethasone daily on days 2, 3, 4 (PO/IV)
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; IV – intravenous; NK1 RA – neurokinin-1 receptor antagonist; PO – by mouth; SQ – subcutaneous Key: * All treatments should be started before chemotherapy; † With or without oral lorazepam, IV or sublingual every 6 hours as needed for days 1-4, with or without H2 blocker or proton pump inhibitor. For regimens containing olanzapine, only use oral lorazepam if needed.	

Table 3. NCCN Recommendations for Acute and Delayed Emesis Prevention for Moderate Emetic Risk Parenteral Anticancer Agents*†[1]

Day 1 (Select option D, E, or F)	Days 2, 3
Treatment option D (preferred) use the following combination: • 5-HT3 RA (PO, SQ, IV) • Dexamethasone once (PO or IV)	Treatment option D: • Dexamethasone daily on days 2, 3 (PO/IV) **OR** • 5-HT3 RA monotherapy daily on days 2, 3

Treatment option E, use the following combination: • Olanzapine orally once • Palonosetron IV once • Dexamethasone once (PO/IV)	Treatment option E: • Olanzapine orally daily on days 2, 3
Treatment option F, use the following combination: • NK1 RA once (PO or IV) • 5-HT3 RA once (PO, SQ or IV) • Dexamethasone once (PO/IV)	Treatment option F: • Aprepitant 80 mg orally on days 2, 3 (if aprepitant orally was used on day 1) +/- Dexamethasone days 2,3 (PO/IV)
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; IV – intravenous; NK1 RA – neurokinin-1 receptor antagonist; PO – by mouth; SQ – subcutaneous Key: * All treatments should be started before chemotherapy; † With or without lorazepam PO, IV or sublingual every 6 hours as needed for days 1-4. With or without H2 blocker or proton pump inhibitor. For regimens containing olanzapine, only use PO lorazepam if needed.	

Table 4. NCCN Recommendations for Acute and Delayed Emesis Prevention for Low Emetic Risk Parenteral Anticancer Agents*†[1]

Repeat daily for multiday doses of chemotherapy
• Dexamethasone once (PO or IV) once OR • Metoclopramide (PO/IV) once OR • Prochlorperazine (PO/IV) once OR • 5-HT3 RA (PO) once
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; IV – intravenous; PO – by mouth; SQ – subcutaneous Key: * All treatments should be started before chemotherapy; † With or without oral lorazepam, IV or sublingual every 6 hours as needed for days 1-4

Oral chemotherapy can have a risk of emesis, and recommendations for antiemetics are separated into high to moderate emetic risk and low to minimal emetic risk (**Table 5**).

Table 5. NCCN Recommendations for Oral Chemotherapy Emesis Prevention*[1]

High to Moderate Emetic Risk	• Start before chemotherapy and continue daily while receiving chemotherapy • 5-HT3 RA recommended (PO or transdermal)
Low to Minimal Emetic Risk	• As-needed antiemetic use is recommended • If nausea or vomiting occurs, start treatment before chemotherapy in future cycles and continue daily • Use metoclopramide orally OR • Prochlorperazine orally OR • 5-HT3 RA orally
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; PO - orally Key: *With or without oral lorazepam, IV or sublingual every 6 hours as needed	

In addition to scheduled emesis prevention, breakthrough treatment for chemotherapy-induced nausea and vomiting may be needed.[1] In general, breakthrough treatment should be from a different drug class than currently used therapy and should be added to current regimen (see options below).[1] If nausea and vomiting is controlled, the medication should be continued on a schedule. If breakthrough nausea/vomiting remains uncontrolled then a dose adjustment should be considered and/or one therapy from another drug class should be added.[1] Re-evaluation of antiemetic therapy should be considered to prevent need for breakthrough therapy and a higher level of primary antiemetic treatment should be used for the next cycle.

Antiemetic choices for breakthrough chemotherapy-induced nausea/vomiting are the following:

- Olanzapine orally (preferred category 1)
- Benzodiazepine orally/sublingual/IV
- Cannabinoid orally
- Haloperidol orally/IV
- Metoclopramide orally/IV
- Scopolamine transdermal patch
- Phenothiazine (prochlorperazine or promethazine)
- 5-HT3 RA orally/transdermal
- Dexamethasone orally/IV

Radiation therapy may also cause nausea/vomiting. Antiemetic therapy for radiation is based on amount of the body that is being irradiated. The use of granisetron orally or ondansetron (+/- dexamethasone orally) should be given to patients as pretreatment for each day patients receive radiation therapy to the upper abdomen/localized sites.[1] For patients receiving total body irradiation, pretreatment for each day of radiation therapy should be with granisetron or ondansetron orally (+/- dexamethasone orally).[1] If the patients is receiving chemotherapy and radiation therapy then recommendations should be based on emetogenicity of chemotherapy regimen.

In patients who experience anticipatory nausea/vomiting, preventative therapy is most important. Recommendations include using optimal antiemetic therapy during every cycle of treatment, avoidance of smells that precipitate treatment, behavioral therapy, acupuncture/acupressure and consideration of anxiolytic therapy.

If patients are receiving multiday emetogenic chemotherapy they may need antiemetic therapy for acute and delayed nausea/vomiting. General therapies include dexamethasone (unless regimen already includes a steroid or olanzapine if the patient can't tolerate dexamethasone), 5-HT3 RAs, and neurokinin-1 receptor antagonists.

After review, one guideline was excluded due to poor quality.[22]

New Formulations/Indications:

CINVANTI (aprepitant) – A new formulation of injectable aprepitant 130 mg was approved in October of 2019.[4] Aprepitant is approved as preventative therapy for the following patients:

- Acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin as a single-dose regimen
- Delayed nausea and vomiting associated with initial and repeat courses of MEC as a single-dose regimen
- Nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen

Cinvanti can be given as an intravenous injection over 2 minutes or as an infusion over 30 minutes, to be completed approximately 30 minutes prior to chemotherapy.

EMEND (fosaprepitant) – Fosaprepitant was approved for the use in pediatric patients 6 months of age and older for prevention of CINV.[5] Fosaprepitant is approved for use, in combination with other antiemetics, for the prevention of acute and delayed nausea and vomiting associated with HEC, including high-dose cisplatin, and for delayed nausea and vomiting associated with initial and repeat courses of MEC. Evidence for the pediatric indication was based off of trials in adults with additional safety, efficacy (3-day oral aprepitant trial completed in pediatrics) and pharmacokinetic data.

Aprepitant - In September of 2019, the indication for the use of aprepitant for the prevention of PONV was removed.[23] Use of aprepitant in studies at non-recommended doses and in patients not using the medication for CINV demonstrated a single case of the following adverse events: angioedema and urticaria, constipation, and sub-ileus. Aprepitant is indicated for use only in patients with CINV.

Palonosetron – Palonosetron received an expanded indication for the use in pediatric patients in December of 2018.[6] The use of palonosetron injection has been approved for use in patients 1 month to less than 17 years of age for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC. A study supporting the indication evaluated 165 pediatric patients given palonosetron 20 mcg/kg (max dose of 1.5 mg) 30 minutes prior to start of chemotherapy.

New FDA Safety Alerts:

Table 5. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Rolapitant[25]	VARUBI	August 2020	Contraindications	Use in pediatric patients less than 2 years of age is contraindicated due to irreversible impairment of sexual development and fertility in juvenile rats.
Fosaprepitant[5]	EMEND	February 2018	Warnings and Precautions	Infusion site reactions (including thrombophlebitis, necrosis, and vasculitis) have occurred. A majority or reactions have been in patients receiving vesicant chemotherapy. Avoid infusion in to small veins. Medication should be discontinued and appropriate treatment administered if severe reaction occurs.

Abbreviated New Drug Review:

Trade Name: Amisulpride (BARHEMSYS)
Indications
• Prevention of PONV, either alone or in combination with an antiemetic of a different class in adult patients.[3] • Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis in adult patients.[3]
Dosage
• Prevention of PONV (alone or in combination): 5 mg as a single intravenous dose (IV) infused over 1 to 2 minutes at the time of induction of anesthesia.[3] • Treatment of PONV: 10 mg as a single IV dose infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure.[3]
Background
Amisulpride is a dopamine-2 antagonist used for prophylaxis and treatment of PONV. First-line treatments recommended for surgical prophylaxis are $5HT_3$ RAs.[3]
Efficacy
Prophylaxis: Prevention of PONV was studied in 2 double-blind, placebo-controlled, randomized controlled trials in patients scheduled for elective surgery with general anesthesia.[3] Amisulpride was given as monotherapy in the first study in patients with 2-4 risk factors for PONV and as combination therapy in the second study (administered with ondansetron, dexamethasone or betamethasone) in patients with 3-4 risk factors for PONV. The primary endpoint in both studies was a complete response which was defined as absence of any episodes of emesis or use of rescue medication within the first 24 hours after treatment. Results: - Forty-four percent of patients treated with amisulpride had a complete response compared to 33% in the placebo group in the first study (unadjusted mean difference [MD] 12%; 95% CI, 2% to 22%; ARR 11%/NNT 9).[3] - In the second study, 58% of patients had a complete response compared to 47% in the placebo group (MD 13%; 95% CI, 5% to 22%; ARR 13%/NNT 8).[3] Treatment: Amisulpride was studied in two double-bind, placebo-controlled, multi-center, randomized controlled trials in patients with PONV following elective surgery with general anesthesia. The first study was in patients, with 2-3 risk factors for PONV, who had not received any prophylactic treatment for PONV. In the second study, patients with 3-4 risk factors for PONV had been treated and failed therapy with an antiemetic from another class ($5HT_3$ antagonists, dexamethasone or other antiemetic) for PONV for current procedure. A complete response was the primary endpoint in both studies, which was defined as absence of any episodes of emesis or use of rescue medication within the first 24 hours after treatment (excluding emesis within the first 30 minutes). Results: - A complete response was demonstrated in 31% of patients treated with amisulpride in the first study compared to 22% of patients treated with placebo (treatment naïve study) (MD 10%; 95% CI, 1% to 19%; ARR 10%/NNT 10).[3,26] - A complete response was demonstrated in 42% of patients treated with amisulpride in the second study compared to 29% treated with placebo (prior prophylaxis study) (MD 13%; 95% CI, 5% to 22%; ARR 13%/NNT 8).[3]
Safety
The most common adverse events that occurred in 2% or more of patients taking amisulpride for PONV prevention were the following: increased blood prolactin concentrations, chills, hypokalemia, procedural hypotension and abdominal distention. The use of amisulpride for the treatment of PONV was associated with infusion site reactions as the most common adverse reaction.
Evidence Gaps/Limitations
Amisulpride has only be been studied as a single use injection. There is insufficient evidence for additional doses of amisulpride. Amisulpride has not been studied in pediatric patients.
Recommendation
There is moderate strength of evidence that amisulpride is effective for the treatment and prophylaxis of PONV. Amisulpride is a treatment option for patients not responding or who cannot tolerate current standard of care therapies for PONV.
Abbreviations: ARR – absolute risk reduction; CI – confidence interval; IV – intravenous; MD – mean difference; NNT – number needed to treat; PONV – post-op nausea and vomiting

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
ondansetron	ONDANSETRON ODT	TAB RAPDIS	PO	Y
ondansetron HCl	ONDANSETRON HCL	SOLUTION	PO	Y
ondansetron HCl	ONDANSETRON HCL	TABLET	PO	Y
ondansetron HCl	ZOFRAN	TABLET	PO	Y
aprepitant	APREPITANT	CAP DS PK	PO	N
aprepitant	EMEND	CAP DS PK	PO	N
aprepitant	APREPITANT	CAPSULE	PO	N
aprepitant	EMEND	CAPSULE	PO	N
aprepitant	EMEND	SUSP RECON	PO	N
dolasetron mesylate	ANZEMET	TABLET	PO	N
doxylamine succinate/vit B6	BONJESTA	TAB IR DR	PO	N
doxylamine succinate/vit B6	DICLEGIS	TABLET DR	PO	N
doxylamine succinate/vit B6	DOXYLAMINE SUCC-PYRIDOXINE HCL	TABLET DR	PO	N
granisetron	SUSTOL	LIQ ER SYR	SQ	N
granisetron	SANCUSO	PATCH TDWK	TD	N
granisetron HCl	GRANISETRON HCL	TABLET	PO	N
netupitant/palonosetron HCl	AKYNZEO	CAPSULE	PO	N

ondansetron	ZUPLENZ	FILM	PO	N
rolapitant HCl	VARUBI	TABLET	PO	N
amisulpride	BARHEMSYS	VIAL	IV	
aprepitant	CINVANTI	VIAL	IV	
fosaprepitant dimeglumine	EMEND	VIAL	IV	
fosaprepitant dimeglumine	FOSAPREPITANT DIMEGLUMINE	VIAL	IV	
fosnetupitant/palonosetron	AKYNZEO	VIAL	IV	
granisetron HCl	GRANISETRON HCL	VIAL	IV	
granisetron HCl/PF	GRANISETRON HCL	VIAL	IV	
ondansetron HCl	ONDANSETRON HCL	VIAL	IV	
ondansetron HCl in 0.9 % NaCl	ONDANSETRON HCL-0.9% NACL	PIGGYBACK	IV	
Ondansetron HCl in D5W	ONDANSETRON HCL-D5W	PIGGYBACK	IV	
ondansetron HCl/PF	ONDANSETRON HCL	AMPUL	IJ	
ondansetron HCl/PF	ONDANSETRON HCL	SYRINGE	IJ	
ondansetron HCl/PF	ONDANSETRON HCL	VIAL	IJ	
palonosetron HCl	PALONOSETRON HCL	SYRINGE	IV	
palonosetron HCl	ALOXI	VIAL	IV	
palonosetron HCl	PALONOSETRON HCL	VIAL	IV	

Appendix 2: New Comparative Clinical Trials

A total of ninety-five citations were manually reviewed from the initial literature search. After further review, ninety-five citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 09, 2020
Search Strategy:

#	Searches	Results
1	ondansetron.mp. or Ondansetron/	5125
2	aprepitant.mp. or Aprepitant/	1121
3	dolasetron.mp.	309
4	doxylamine.mp. or Doxylamine/	515
5	granisetron.mp. or Granisetron/	1785
6	netupitant.mp.	152
7	rolapitant.mp.	90
8	amisulpride.mp. or Amisulpride/	1357
9	fosaprepitant.mp.	174
10	palonosetron.mp. or Palonosetron/	765
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	9621
12	limit 11 to (english language and humans)	5631
13	limit 12 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	375
14	limit 13 to yr="2017 -Current"	95

Appendix 4: Key Inclusion Criteria

Population	Pediatric and adult patients with nausea and/or vomiting requiring an antiemetic, including indication such as post-op nausea and vomiting and chemotherapy induced nausea and vomiting.
Intervention	Newer antiemetics
Comparator	Active treatments or placebo
Outcomes	Absence of emesis or emesis reduction, incidence of nausea, need for rescue therapy and quality of life assessments
Timing	Prevention or treatment of nausea/vomiting
Setting	Inpatient and outpatient

Appendix 5: Prior Authorization Criteria

Antiemetics

Goal(s):

- Promote use of preferred antiemetics.
- 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 and 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 and 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 is receiving chemotherapy or radiation?	**Yes:** Approve for up to 6 months.	**No:** Go to #8
8. Does patient have refractory nausea/vomiting 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: *2/21 (KS), 9/17 (KS); 1/17; 1/16; 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03*
Implementation: *TBD; 1/1/18; 4/1/17; 2/12/16; 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*