



Antiemetic Agents Therapeutic Class Review (TCR)

November 16, 2018

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MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
NK₁ receptor antagonists		
aprepitant capsules (Emend®) ¹	generic, Merck	In combination with other antiemetic agents for: <ul style="list-style-type: none"> Acute and delayed nausea and vomiting (N/V) associated with highly emetogenic cancer chemotherapy (initial and repeat dosing), including high-dose cisplatin in patients ≥ 12 years old N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in patients ≥ 12 years old Prevention of post-operative N/V in adults <i>Limitations of use:</i> has not been studied for the treatment of established N/V; chronic continuous administration is not recommended
aprepitant injectable emulsion (Cinvanti™) ²	Heron	In combination with other antiemetic agents for the prevention of: <ul style="list-style-type: none"> Acute and delayed N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin in adults N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in adults <i>Limitation of use:</i> has not been studied for treatment of established N/V
aprepitant suspension (Emend®) ³	Merck	In combination with other antiemetic agents for: <ul style="list-style-type: none"> Acute and delayed N/V associated with highly emetogenic cancer chemotherapy (initial and repeat dosing), including high-dose cisplatin in patients ≥ 6 months old N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in patients ≥ 6 months old Prevention of post-operative N/V in adults <i>Limitations of use:</i> has not been studied for the treatment of established N/V; chronic continuous administration is not recommended
fosaprepitant (Emend® for injection) ⁴	Merck	In combination with other antiemetic agents for: <ul style="list-style-type: none"> Prevention of acute and delayed N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin in patients ≥ 6 months old Prevention of delayed N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in patients ≥ 6 months old <i>Limitation of use:</i> has not been studied for the treatment of established N/V
rolapitant (Varubi™) ^{5 *}	Tesaro	In combination with other antiemetic agents for: <ul style="list-style-type: none"> Prevention of acute and delayed N/V associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
5-HT₃ antagonists		
dolasetron (Anzemet®) ⁶	Validus	<ul style="list-style-type: none"> Prevention of N/V associated with moderately emetogenic cancer chemotherapy; including initial and repeat courses in adults and children ≥ 2 years of age Prevention of post-operative N/V in adults and children ≥ 2 years of age

* Rolapitant (Varubi) injectable emulsion (166.5 mg/92.5 mL) is obsolete; final expiry was September 30, 2018.

FDA-Approved Indications (continued)

Drugs	Manufacturer	Indication(s)
5-HT₃ antagonists (continued)		
granisetron ^{7,8}	generic	<ul style="list-style-type: none"> Prevention of N/V associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin Prevention of N/V associated with radiation, including total body irradiation and fractionated abdominal radiation Injection: Prevention and treatment of post-operative N/V in adults
granisetron injection, extended-release (Sustol®) ⁹	Heron	<ul style="list-style-type: none"> In combination with other antiemetics in adults for the prevention of acute and delayed N/V associated in with initial and repeat courses of moderately emetogenic cancer chemotherapy or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens
granisetron transdermal (Sancuso®) ¹⁰	Kyowa	<ul style="list-style-type: none"> Prevention of N/V in patients receiving moderately or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration
ondansetron (Zofran®) ^{11,12}	generic, GlaxoSmithKline/Novartis (Zofran®)	<ul style="list-style-type: none"> Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Prevention of post-operative N/V
ondansetron soluble film (Zuplenz®) ¹³	Galena/Midatech (Zuplenz)	<ul style="list-style-type: none"> Prevention of N/V associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m² Prevention of N/V associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen
palonosetron (Aloxi®) ¹⁴	generic, Eisai	<ul style="list-style-type: none"> Prevention of acute and delayed N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Prevention of acute N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy Prevention of post-operative N/V for up to 24 hours following surgery
Combination products		
fosnetupitant/palonosetron injectable (Akynzeo®) ¹⁵	Helsinn	<ul style="list-style-type: none"> In combination with dexamethasone in adults, for the prevention of acute and delayed N/V associated with initial and repeat courses of highly emetogenic chemotherapy <p><i>Limitation of use:</i> fosnetupitant/palonosetron has not been studied for the prevention of N/V associated with anthracycline plus cyclophosphamide chemotherapy</p>
netupitant/palonosetron capsule (Akynzeo®) ¹⁶	Helsinn	<ul style="list-style-type: none"> In combination with dexamethasone in adults, for the prevention of acute and delayed N/V associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy

*In July 2018, Novartis reported a planned discontinuation of Zofran (ondansetron) tablets in both 4 mg and 8 mg strengths to the United States (U.S.) Food and Drug Administration (FDA); however, product may remain until supply is depleted.

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Cannabinoids		
dronabinol (Marinol®) ¹⁷	generic, Abbvie	<ul style="list-style-type: none"> ▪ Treatment of N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments ▪ Anorexia associated with weight loss in patients with AIDS
dronabinol (Syndros) ¹⁸	Insys	<ul style="list-style-type: none"> ▪ Treatment of N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments ▪ Anorexia associated with weight loss in patients with AIDS
nabilone (Cesamet®) ¹⁹	Meda/Mylan	<ul style="list-style-type: none"> ▪ Treatment of N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
Antidopaminergic Agents		
metoclopramide oral disintegrating tablets ²⁰	generic	<ul style="list-style-type: none"> ▪ Relief of heartburn symptoms of refractory gastroesophageal reflux disease (GERD) when other treatments do not work ▪ Relief of symptoms of slow stomach emptying in patients with diabetes (diabetic gastroparesis)
metoclopramide (Reglan®) ^{21,22}	generic, ANI	<ul style="list-style-type: none"> ▪ Relief of symptoms associated with acute and recurrent diabetic gastroparesis ▪ Prevention of N/V associated with emetogenic cancer chemotherapy ▪ Prevention of post-operative N/V ▪ Small bowel intubation ▪ As short-term therapy for adults with symptomatic, documented gastroesophageal reflux (GERD) who fail to respond to conventional therapy
Antihistamines		
doxylamine/pyridoxine (Diclegis®, Bonjesta™) ^{23,24}	Duchesnay	<ul style="list-style-type: none"> ▪ Treatment of N/V of pregnancy in women who do not respond to conservative management
Others		
phosphorated carbohydrate solution (Emetrol® OTC) ²⁵	Wellspring	<ul style="list-style-type: none"> ▪ Relief of nausea due to upset stomach from intestinal flu, stomach flu, and food or drink indiscretions
trimethobenzamide (Tigan®) ^{26,27}	generic, Monarch, Par	<ul style="list-style-type: none"> ▪ Treatment of N/V associated with gastroenteritis

OVERVIEW

Chemotherapy-induced vomiting (emesis) and nausea can significantly impact a patient's quality of life, leading to poor compliance with future chemotherapy or radiation treatments. In addition, nausea and vomiting can lead to several adverse events, such as nutrient depletion, metabolic imbalances, erosion of self-care, anorexia, diminished performance and mental status, wound dehiscence, tears in the esophagus, and cessation of potentially useful or curative cancer treatment. Approximately 70% to 80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting, whereas 10% to 44% experience anticipatory nausea and/or vomiting.²⁸ Furthermore, more than 90% of patients using highly emetogenic chemotherapeutic agents will experience acute emesis; however, only

approximately 30% of these patients will experience a vomiting episode if they receive an antiemetic prior to their highly emetogenic chemotherapeutic treatment.²⁹

There are several different factors that influence the incidence and severity of nausea and vomiting due to chemotherapy or radiation, including the specific chemotherapy medication(s) used, emetogenic potential of the chemotherapy agent(s), dose of chemotherapy agent(s), chemotherapy regimen and route of administration, amount and location of radiation therapy, and the individual patient response.^{30,31}

The goal of antiemetic therapy is to prevent nausea and vomiting (N/V) completely.^{32,33} With current agents, complete control of emesis (e.g., no vomiting) is achievable in the majority of patients in the first 24 hours and approximately 45% of patients during the first week of chemotherapy. Even though vomiting can often be prevented or reduced significantly using prophylactic antiemetic medications, nausea is often times much harder to control. Complete control correlates highly with patient perception of emesis and with patient satisfaction with their emetic control.

Nausea, the perception that emesis may occur, can be judged only by the patient. Nausea is quantified by the use of various questionnaires, such as visual analog scales (VAS).^{34,35,36} The incidence of nausea correlates well with the incidence of vomiting, although chemotherapy-induced nausea occurs at a greater frequency.^{37,38} Total control (no nausea or vomiting) is ideal, but lesser control rates, such as major control (fewer than 3 emetic episodes) or minor control (3 to 5 emetic episodes), may still have some value in difficult emetic situations. The prevention of delayed emesis and anticipatory emesis is equal in importance to the need to prevent acute (within first 24 hours) chemotherapy- and radiation-induced emesis.^{39,40}

The 2017 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the choice of antiemetic treatment should be based on the chemotherapy agent with the greatest degree of emetic risk.⁴¹ The revision includes medications not previously available during the last guideline update, such as additional dosage forms of granisetron (extended-release injection; Sustol) and rolapitant (Varubi). Likewise, choice of antiemetic treatment should be based on the agent with the greatest degree of emetic risk in patients receiving both chemotherapy and radiotherapy. Optimal treatment should be used with initial chemotherapy to limit anticipatory nausea and vomiting. Patients with minimal emesis risk should not be routinely offered antiemetic prophylaxis. For low-emetic-risk chemotherapy regimens, adults should be offered a single dose of a 5-HT₃ antagonist or a single 8 mg dose of dexamethasone prior to treatment. For patients receiving moderately emetogenic chemotherapy (MEC), ASCO recommends treatment with a 2-drug combination of a 5-HT₃ antagonist and dexamethasone (day 1). Those receiving MEC and treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/minute should receive a 3-drug combination, including an NK₁ antagonist, 5-HT₃ antagonist, and dexamethasone. Those using MEC regimens with known delayed nausea and vomiting should also receive additional dexamethasone on days 2 to 3. Previously, the preferred type-3 serotonin (5-HT₃) receptor antagonist for patients receiving MEC was palonosetron (Aloxi; day 1), however, the revised guidelines state that any 5-HT₃ antagonist is acceptable. ASCO recommends that all patients who receive highly emetogenic chemotherapy (HEC), including cisplatin and other highly emetogenic single agents, should be offered a 4-drug combination of an NK₁ receptor antagonist (duration based on formulation), a 5-HT₃ receptor antagonist (day 1), dexamethasone (days 1 through 4), and olanzapine (days 1 through 4). ASCO recommends that all patients who receive an anthracycline plus cyclophosphamide should also be offered a 4-drug combination of a NK₁ receptor antagonist (duration based on formulation), a 5-HT₃ receptor antagonist (day 1), dexamethasone (days 1 through 4), and

olanzapine (days 1 through 4). Patients with breakthrough nausea and vomiting despite optimal prophylaxis, including olanzapine, may be offered an additional drug from another class for subsequent treatments (those who did not receive olanzapine should be offered olanzapine first). For multiday chemotherapy, after assessing emetic risk of the agents prescribed, patients should receive an agent of highest therapeutic index daily during chemotherapy and for 2 days thereafter. Lorazepam may be a useful adjunctive therapy, but it is not recommended as a single agent. Evidence remains insufficient to provide a recommendation regarding treatment with medical marijuana or its use in place of FDA-approved cannabinoids. Those receiving highly emetogenic radiation therapy should receive a 5-HT₃ receptor antagonist and dexamethasone before each fraction and on the day after each fraction, even if radiation therapy is not planned for that day. A 5-HT₃ receptor antagonist with or without dexamethasone prior to each fraction also is recommended before moderately emetogenic radiation therapy for the first 5 fractions. Patients with select low-emetogenic risk radiation therapy should be offered dexamethasone, with other alternatives considered for rescue therapy based on prior treatment and location of radiation. In pediatrics receiving HEC, ASCO recommends treatment with a 5-HT₃ receptor antagonist, aprepitant (if eligible), and dexamethasone, noting that higher weight-based dosing may be necessary. In pediatrics receiving MEC, ASCO recommends treatment with a 5-HT₃ receptor antagonist and dexamethasone. Pediatric patients receiving HEC who are unable to receive dexamethasone should receive palonosetron and aprepitant. Fosnetupitant was not available at the time these guidelines were developed.

The v3.2018 National Comprehensive Cancer Network (NCCN) guidelines state that the choice of antiemetic should be based on emetic risk of the chemotherapy, prior experience with antiemetics, as well as patient factors.⁴² Furthermore, the guidelines state that antiemetic therapy should be initiated prior to the start of chemotherapy to provide maximal protection against chemotherapy-induced emesis. In addition, the antiemetic therapy should be continued for the same timeframe as the duration of the emetic activity of the chemotherapeutic agent being used. The guidelines identify emesis prevention treatment options for high, moderate, low, and minimal emetic risk intravenous (IV) chemotherapy, oral chemotherapy, and radiation therapy, as well as breakthrough treatment for chemotherapy-induced N/V. To prevent acute and delayed emesis in patients receiving IV HEC (including any chemotherapy regimen that contains an anthracycline and cyclophosphamide or carboplatin AUC ≥ 4 mg/mL/minute), NCCN recommends multiple regimen options without preference (Category 1). In general, these consist of a 3- or 4-drug combination of an NK₁ receptor antagonist (duration and dosing is dependent on formulation), a 5-HT₃ receptor antagonist (day 1), and dexamethasone (days 1 through 4), with or without olanzapine (days 1 through 4). A 3-drug regimen of olanzapine, palonosetron, and dexamethasone may also be used. To prevent acute and delayed emesis in patient receiving IV MEC (including carboplatin AUC < 4 mg/mL/minute), NCCN recommends a 5-HT₃ antagonist and dexamethasone as a 3 day regimen. A NK₁ antagonist should be added for select patients with additional risk factors or previous treatment failures with a steroid and 5-HT₃ antagonist alone, in which case, the regimen may range from 1 to 3 days based on the treatment regimen selected. NCCN does not specify one 5-HT₃ antagonist or NK₁ antagonist over another (or route/formulation). Equivalent alternatives to this include 3-day olanzapine-containing regimens (olanzapine, palonosetron, and dexamethasone) (all Category 1). For IV low emetogenic risk chemotherapy, dexamethasone, metoclopramide (Reglan), prochlorperazine (Compazine®, Compro®), or an oral 5-HT₃ antagonist may be used and repeated daily for multiday doses of chemotherapy. There is no routine prophylaxis for patients who receive minimal emetic risk IV chemotherapy. Providers are encouraged to follow all guideline recommendations especially for minimal and low emetic risk to

avoid overuse of prophylactic antiemetics. Overuse of antiemetic therapy may expose the patient to unnecessary adverse drug reactions. For patients who receive oral chemotherapy with a high or moderate emetic risk, an oral or transdermal 5-HT₃ antagonist should be initiated prior to chemotherapy. Conversely, for patients who receive oral chemotherapy with a low to minimal emetic risk, patients may receive alternative oral agents as needed, such as metoclopramide, prochlorperazine, or an oral 5-HT₃ receptor antagonist. For breakthrough treatment of chemotherapy-induced N/V, the general principle is to add 1 agent from a different class, as needed, to the existing regimen (e.g., antipsychotic, benzodiazepine, cannabinoid, dopamine receptor antagonist, phenothiazine, 5-HT₃ antagonist, scopolamine patch, or corticosteroid). Based on response to the breakthrough treatment, the antiemetic therapy is adjusted and/or modified and may be scheduled or administered on an as needed basis. For radiation-induced N/V associated with upper abdomen/localized sites or total body irradiation, NCCN recommends oral granisetron or ondansetron with or without oral dexamethasone as pretreatment for each day of radiation therapy. For patients receiving chemotherapy and radiation therapy, NCCN recommends the emesis prevention regimen for chemotherapy-induced N/V. Details on dosing and duration are dependent on the formulation and regimen selected and are detailed in the NCCN guidelines.

The American Society of Anesthesiologists has published recommendations on the prevention of post-operative nausea and vomiting (PONV) within their guidelines on postanesthetic care.⁴³ They recommend routine assessment and monitoring for N/V. For prophylaxis and treatment of N/V, they evaluated the following classes of medication and rated them based on the quality of evidence (range of A to C, from randomized controlled trials to informal opinion and determination of beneficial [B] or equivocal [E]): antihistamines (Category A3-B evidence), 5-HT₃ receptor antagonists (Category A1-B evidence as a class), tranquilizers/neuroleptics (e.g., droperidol [Category A1-B evidence], haloperidol [Category A2-B evidence], hydroxyzine [Category A3-B evidence], perphenazine [Category A3-B evidence], prochlorperazine [Category A1-E evidence]). For prophylaxis of PONV using multiple agents, they determined that multiple agents may be used when needed (Category A2-B evidence). They further note that pharmacologic treatment of N/V is recommended as it improves patient satisfaction and comfort and reduces time to discharge.

Nausea and vomiting of pregnancy “morning sickness,” which can occur at any time of day, can affect pregnant women with varying symptoms from nausea to severe vomiting. Lifestyle changes for women with nausea and vomiting of pregnancy include rest, avoiding nauseating stimuli, eating small, frequent low fat meals that are low in spices.⁴⁴ According to the American College of Obstetricians and Gynecologists (ACOG) 2018 Practice Bulletin, prompt treatment of N/V of pregnancy is important to prevent hyperemesis gravidarum, and first-line treatment of N/V of pregnancy consists of nonpharmacologic options (e.g., assessing supplementation change options, ginger capsules, acupressure).⁴⁵ For persistent symptoms, pharmacologic treatment with vitamin B6 (pyridoxine) or vitamin B6 plus doxylamine, including co-formulated products such as Diclegis or Bonjesta, are recommended.^{46,47} If symptoms continue to persist, other medications can be considered for off-label use. Notably, ACOG states that no single method has demonstrated superiority over another and that treatment options within each step are presented alphabetically rather than in any preference order. Diclegis, a fixed-dose combination of the antihistamine doxylamine 10 mg plus pyridoxine 10 mg, is the first FDA-approved, pregnancy category A delayed-release combination medication for the treatment of N/V of pregnancy. Bonjesta, is a higher strength (20 mg/20 mg) extended-release doxylamine/pyridoxine fixed-dose combination, without any significant relationships between fetal abnormalities and use in the first trimester.

Dronabinol (Syndros) and nabilone (Cesamet) are Schedule II controlled substances and dronabinol (Marinol) is a Schedule III controlled substance as classified by the Drug Enforcement Agency (DEA).

PHARMACOLOGY^{48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72}

NK₁ receptor antagonists (aprepitant [Emend, Cinvanti], fosaprepitant [Emend for Injection], rolapitant [Varubi])

Aprepitant (Emend, Cinvanti) exerts its main antiemetic action by occupying brain substance P-NK₁ receptors. This receptor pathway regulates the behavioral responses to a range of noxious and stressful stimuli. Expression in the brainstem emetic nuclei has implicated substance P in the control of vomiting.⁷³ Aprepitant has little or no affinity for 5-HT₃, dopamine, or corticosteroid receptors. Fosaprepitant (Emend for injection) is a prodrug of aprepitant and is quickly converted to aprepitant when administered IV.

Rolapitant (Varubi) is a selective and competitive antagonist of substance P-NK₁ receptors and also has little or no affinity for other receptors.

5-HT₃ antagonists (dolasetron [Anzemet], granisetron, granisetron extended-release injection [Sustol], granisetron transdermal [Sancuso], ondansetron [Zofran, Zuplenz], palonosetron [Aloxi])

Dolasetron (Anzemet), granisetron (generic, Sancuso, Sustol), ondansetron (Zofran, Zuplenz), and palonosetron (Aloxi) selectively block 5-HT₃ receptors. While the mechanism of action of these drugs has not been fully elucidated, they are not D₂ receptor antagonists. Serotonin receptors of the 5-HT₃ type are found centrally in the chemoreceptor trigger zone (CTZ) and peripherally at vagal nerve terminals in the intestines. It has not been determined whether the antiemetic action of the 5-HT₃ antagonists is mediated centrally, peripherally, or a combination of both sites. N/V during chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. The released serotonin may stimulate vagal afferents through the 5-HT₃ receptors and initiate the vomiting reflex.

Combination products (fosnetupitant/palonosetron [Akynzeo], netupitant/palonosetron [Akynzeo])

Oral Akynzeo contains netupitant, a NK₁ receptor antagonist, and palonosetron, a 5-HT₃ antagonist. Fosnetupitant is a prodrug of netupitant and is found in the injectable formulation of Akynzeo, which is also co-formulated with palonosetron. These combination products exert their effect by occupying brain substance P-NK₁ receptors and selectively blocking 5-HT₃ receptors as mentioned above in the NK₁ receptor antagonist and 5-HT₃ antagonists sections.

Cannabinoids (dronabinol [Marinol, Syndros], nabilone [Cesamet])

Dronabinol (Marinol, Syndros) and nabilone (Cesamet) act on the cannabinoid receptors (CB1 and CB2) in the brain.⁷⁴ These receptors are believed to regulate nausea and vomiting. Like most cannabinoids, these agents have complex effects on the central nervous system (CNS) and may even exert central sympathomimetic activity.

Antidopaminergics (metoclopramide [Reglan, Metozolv ODT])

Metoclopramide (Reglan, Metozolv ODT) aids in gastric motility, increasing emptying and intestinal transit. Antiemetic properties are due to its effects on central and peripheral dopamine receptors. It blocks dopaminergic activity to the medullary chemoreceptor trigger zone.

Antihistamines (doxylamine/pyridoxine [Diclegis, Bonjesta])

Histaminergic (H1) antagonists act on the vomiting center and vestibular pathways making them effective in the prevention and treatment of motion sickness induced N/V. The mechanism of action of the antihistamine doxylamine and the vitamin B6 (pyridoxine) combination (Diclegis) is unknown for the treatment of N/V of pregnancy.

Others (phosphorated carbohydrate solution [Emetrol OTC] and trimethobenzamide [Tigan])

Phosphorated carbohydrate relieves nausea through a direct, local action, theoretically by inhibiting gastric emptying and reducing gastric tone.

The mechanism of action of trimethobenzamide is unknown, but it may mediate the CTZ.

PHARMACOKINETICS^{75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99}

Drug	Bioavailability (%)	Half-life (t _{1/2}) (hr)	Metabolites	Excretion (%)	
NK₁ receptor antagonist					
aprepitant (Emend)*	60 – 65	9 – 13	7, weakly active	urine: 57 feces: 45	
aprepitant injectable emulsion (Cinvanti)	--			nr	
fosaprepitant (Emend for injection)	--	9 – 13	prodrug converted to aprepitant	urine: 57 feces: 45	
rolapitant (Varubi) [†]	91 (IV)	169 – 183 (oral) 138-205 (IV)	M19, active	urine: 14.2 (oral) feces: 73 (oral)	
5-HT₃ antagonists					
dolasetron (Anzemet)	75	8.1	hydrodolasetron, active	oral	urine: 61 feces: 39
granisetron	--	6.2 (oral) 4.91–8.95 (IV)	yes, activity questionable	oral	urine: 48 feces: 38
				IV	urine: 49 feces: 34
granisetron injection, extended-release [‡] (Sustol)	--	≈24	yes, activity questionable	urine: 12 (unchanged); 49 (metabolites) feces: 34	

hr = hour; nr = not reported

* Data for oral capsules

[†] Bioequivalence of a single IV infusion of rolapitant 166.5-mg administered over 30 minutes to a single rolapitant 180-mg oral dose was demonstrated in healthy volunteers.¹⁰⁰ The incidence adverse events, all mild or moderate in severity, was similar in the IV and oral groups.

[‡] Utilizes polymer-based drug delivery system which releases granisetron from polymer over an extended period of time.

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (t _{1/2}) (hr)	Metabolites	Excretion (%)
5-HT₃ antagonists (continued)				
granisetron transdermal (Sancuso)	--	N/A; 66% is released from patch over 7 days	yes	urine: 49 feces: 34
ondansetron (Zofran, Zuplenz)	56 (oral)	3.1–6.2 (oral) 2.5–6.7 (IV)	yes, none significant	urine: 5
palonosetron (Aloxi)	--	≈40	yes	feces: 5 to 8 urine: 80
Combination Products				
fosnetupitant/palonosetron (Akyzneo)	--	0.75 ± 0.4 (fosnetupitant) 58 ± 27 (palonosetron)	yes, weakly active (following conversion to netupitant)	feces: 5 to 8 (palonosetron) urine: 85 to 93 (palonosetron)
netupitant/palonosetron (Akyzneo)	97 (palonosetron)	80 ± 29 (netupitant) 50 ± 16 (palonosetron)	yes, weakly active	feces: 70.7 (netupitant); 5 to 8 (palonosetron) urine: 3.95 (netupitant); 85 to 93 (palonosetron)
Cannabinoids				
dronabinol (Marinol, Syndros)	10–20 [§]	25–36	yes, 1 active	urine: 10 to 15 feces: 50
nabilone (Cesamet)	5–20	2–35	yes, active and inactive	urine: 24 feces: 60
Antidopaminergics				
metoclopramide (Metozolv ODT)	65–95	5–6	none	urine: 85 feces: 2
metoclopramide (Reglan)				
Antihistamines				
doxylamine/pyridoxine (Diclegis, Bonjesta)	--	doxylamine – 11.9–12.5 pyridoxine – 0.4–0.5	doxylamine – yes pyridoxine – prodrug	--
Others				
phosphorated carbohydrate solution (Emetrol OTC)	--	--	--	--
trimethobenzamide (Tigan)	60–100	7–9	yes, 1 active	urine: 30 to 50

hr = hour

§ A dose of 4.2 mg of Syndros provides comparable exposure as a 5 mg dronabinol capsule under fasted conditions.

CONTRAINDICATIONS/WARNINGS^{101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125}

Aprepitant (Emend, Cinvanti) and fosaprepitant (Emend for injection) are contraindicated in patients who are hypersensitive to any component of the product. Known hypersensitivity reactions that may occur following use include flushing, erythema, dyspnea, hypotension, syncope, anaphylaxis, and anaphylactic shock. Aprepitant and fosaprepitant should not be used concurrently with pimozide. Inhibition of CYP3A4 by aprepitant or fosaprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. Proteinuria has been reported in 6.8% of patients receiving aprepitant (Emend) in clinical trials. Infusion site reactions have been reported with fosaprepitant. The majority of serious reactions, including thrombophlebitis and vasculitis (and cases leading to necrosis or persisting > 2 weeks), occurred with concomitant vesicant chemotherapy and during the first to third injections; avoid using fosaprepitant injections via small veins or butterfly catheters. If a reaction occurs, the infusion should be discontinued.

Rolapitant (Varubi) is contraindicated in patients taking CYP2D6 substrates with a narrow therapeutic window (e.g., pimozide, thioridazine). It also carries a warning regarding the interaction between rolapitant and other CYP2D6 substrates. The inhibitory effect of rolapitant on CYP2D6 can last for at least 28 days. Other drug interactions involving warnings include warfarin and hormonal contraceptives. The FDA issued a provider alert advising healthcare providers to monitor for hypersensitivity or anaphylaxis in all patients receiving injectable rolapitant both during and following its administration.¹²⁶ Serious hypersensitivity reactions have been reporting in the postmarketing setting.

There is no clinical data for the use of aprepitant (Emend, Cinvanti) in patients with severe hepatic impairment and, therefore, caution should be used when administering aprepitant to these patients.

5-HT₃ receptor antagonists are contraindicated in patients with known hypersensitivity to the drug or any of its components. Cross hypersensitivity reactions have been reported in patients who received other selective 5HT₃ receptor antagonists. The labeling for dolasetron (Anzemet) does not include hypersensitivity to other selective 5HT₃ receptor antagonists as a contraindication. Due to the extended-release of granisetron (Sustol), hypersensitivity reactions may be delayed (7 days or longer). Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving fosnetupitant/palonosetron (Akynzeo) and netupitant/palonosetron (Akynzeo) with or without known hypersensitivity to other 5-HT₃ receptor antagonists, alone but also with concomitant serotonergic drugs.

5-HT₃ receptor antagonists should be administered with caution in patients who have or may develop arrhythmias or prolongation of cardiac conduction intervals, particularly QTc. Electrocardiogram (ECG) changes have occurred in patients using ondansetron (Zofran, Zuplenz) and dolasetron (Anzemet), including QT interval prolongation and torsades de pointes; therefore, the use of ondansetron and dolasetron should be avoided in patients with congenital long QT syndrome. ECG monitoring should also be performed in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking other medications, which increase the risk of QT prolongation. Dolasetron should be used with caution in patients with hypomagnesium, hypokalemia, or congenital long QT syndrome. Hypomagnesium and hypokalemia should be corrected prior to beginning dolasetron therapy and monitored thereafter. Dolasetron may cause dose dependent prolongation of

the PR, QRS, and QT interval and second and third degree atrioventricular block, cardiac arrest, and serious ventricular arrhythmias may occur.

Serotonin syndrome has been reported with 5-HT₃ receptor antagonists (including fosnetupitant/palonosetron and netupitant/palonosetron due to the palonosetron component) alone, but the risk may be higher with concomitant use of other serotonergic drugs. Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs. Granisetron and ondansetron do not stimulate gastric or intestinal peristalsis. They should not be used instead of nasogastric suction. Use of these agents in patients following abdominal surgery or in chemotherapy-induced N/V may mask a progressive ileus and/or gastric distention. Granisetron injection (generic) contains benzyl alcohol and has been associated with serious adverse reactions and death, especially in neonates. Patients should be monitored for constipation and decreased bowel activity, and bowel regimens should be optimized as clinically appropriate. Patients should be advised of signs and symptoms of ileus and report these to a healthcare professional immediately. Injection site reactions including, but not limited to, infection, bleeding, pain, nodules, swelling and induration, have been reported with granisetron extended-release injection (Sustol). These reactions may be delayed (≥ 2 weeks). Increased bruising or hematoma may occur when patients are also using antiplatelet agents or anticoagulants.

Patients with phenylketonuria should be informed that ondansetron orally disintegrating tablets (Zofran ODT, Zuplenz) contain < 0.03 mg phenylalanine in both the 4 mg and 8 mg tablets.

The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness with coadministration.

Dronabinol (Marinol, Syndros) is contraindicated in patients with any known sensitivities to dronabinol, cannabinoid oil (Marinol), sesame oil (Marinol), or any other of its ingredients. Nabilone (Cesamet) is contraindicated in patients with a hypersensitivity to any cannabinoid. Syndros is also contraindicated in patients who are currently receiving or have received disulfiram and or metronidazole-containing products within the last 14 days. Syndros should be avoided in those with a hypersensitivity reaction to alcohol.

Adverse psychiatric effects can persist for 48 to 72 hours following discontinuation of nabilone. Cautious use of both cannabinoids in patients with current or previous psychiatric disorders (e.g., manic depression, depression, and schizophrenia) is recommended. Nabilone can have adverse effects on the central nervous system (CNS) including dizziness, drowsiness, euphoria, disorientation, depression, hallucinations, anxiety, and psychosis. Concomitant use with CNS depressants may increase these effects.

Cautious use of the cannabinoids is recommended also in patients with a history of substance abuse and dependence.

Although a causal relationship has not been established, dronabinol may lower the seizure threshold; therefore, it should be used with caution in patients with a history of seizure disorder.

Dronabinol and nabilone should be used with caution in patients with cardiac disorders due to occasional hypotension, possible hypertension, syncope, or tachycardia.

Patients receiving treatment with dronabinol and nabilone should be specifically warned not to drive, operate machinery, or engage in any hazardous activity while receiving dronabinol and nabilone.

Metoclopramide (Reglan, Metozolv ODT) is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug. Metoclopramide should not be used in epileptics or patients receiving other drugs that are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased. Neonates, infants, children, and adolescents are more likely to experience extrapyramidal side effects.

Metoclopramide should not be used in patients with conditions in which stimulation of the gastrointestinal track is of concern.

Mental depression has occurred with metoclopramide in patients with and without prior history of depression.

Patients with pre-existing Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Metoclopramide has a boxed warning that chronic long-term or high-dose use can lead to increased risk of tardive dyskinesia, involuntary and repetitive movements of the body, even after the drug has been discontinued. Treatment with metoclopramide for longer than 12 weeks is not recommended

There have been rare reports of an uncommon, but potentially fatal, symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) associated with metoclopramide.

Patients with cirrhosis or congestive heart failure may be at risk for fluid retention and volume overload due to an increase in plasma aldosterone. If fluid retention or volume overload occurs, metoclopramide therapy should be discontinued.

Trimethobenzamide (Tigan) injection is contraindicated in pediatric patients and in patients with known hypersensitivity to trimethobenzamide. Trimethobenzamide may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. In disorders such as acute febrile illness, encephalitis, gastroenteritis, dehydration, and electrolyte imbalance, caution should be exercised in administering trimethobenzamide, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). The antiemetic effects of trimethobenzamide may obscure the cause of vomiting in various disorders, such as appendicitis, and may mask the symptoms of overdose of other drugs.

Doxylamine/pyridoxine (Diclegis, Bonjesta) is contraindicated in patients hypersensitive to doxylamine succinate, other ethanolamine derivative antihistamines, or pyridoxine hydrochloride. Doxylamine/pyridoxine is contraindicated in concomitant use with monoamine oxidase (MAO) inhibitors due to an intensification and prolongation of CNS effects. Doxylamine/pyridoxine may cause somnolence and patients should avoid engaging in activities requiring complete mental alertness, such as driving, until cleared to do so by their healthcare provider. Due to the anticholinergic antihistamine component, it is not recommended to be used with CNS depressants, including alcohol, and should be used with caution in patients with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction. **False positives on urine drug screening for methadone, opiates, and phencyclidine phosphate (PCP) have been reported with doxylamine/pyridoxine.**

DRUG INTERACTIONS^{127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151}

aprepitant (Emend, Cinvanti), fosaprepitant (Emend for Injection), and rolapitant (Varubi)

Aprepitant (Emend, Cinvanti) and fosaprepitant (Emend for injection) should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents, which are primarily metabolized through CYP3A4. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than its effect on the pharmacokinetics of IV CYP3A4 substrates. Weak inhibition of CYP enzymes by 40 mg doses of aprepitant is not expected to affect concentration of other drugs to a significant degree. Higher aprepitant doses and repeat doses may produce a clinically significant effect. Moderate inhibition of CYP3A4 by aprepitant 125/80 mg and weak inhibition of CYP3A4 by fosaprepitant 150 mg may result in increased plasma concentrations of these concomitant medicinals. Coadministration of aprepitant or fosaprepitant with drugs that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, nefazodone, diltiazem, clarithromycin, ritonavir, nelfinavir) may result in increased plasma concentrations of aprepitant. If concomitantly used with CYP3A4 inducers (e.g., rifampin, carbamazepine, and phenytoin), aprepitant concentrations may be reduced and may result in decreased aprepitant efficacy.

CYP2C9 metabolism may be induced by aprepitant. Coadministration of aprepitant or fosaprepitant with warfarin may result in a clinically significant (14%) decrease in international normalized ratio (INR). In patients on warfarin, INR should be closely monitored at 7 to 10 days following initiation of the 3-day regimen of aprepitant with each chemotherapy cycle or after a single aprepitant 40 mg dose for the prevention of N/V.

Coadministration with fosaprepitant or aprepitant may reduce the efficacy of hormonal contraceptives, such as oral contraceptives, transdermal patches, implants, and certain intrauterine devices (IUDs), during and for 28 days following the last dose of either fosaprepitant or aprepitant. Alternative or back-up methods of contraception should be used during treatment with and for 1 month following the last dose of fosaprepitant or aprepitant.

Because administration of aprepitant or fosaprepitant with dexamethasone or methylprednisolone approximately doubles the area-under-the-curve (AUC) of the corticosteroid, doses of corticosteroid should be reduced by 50% when co-administered with aprepitant.¹⁵²

Chronic continuous use of fosaprepitant for prevention of N/V is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Concomitant use of benzodiazepines with aprepitant or fosaprepitant may increase benzodiazepine concentrations; therefore, close monitoring and potential benzodiazepine dose reduction may be warranted.

As described above, rolapitant (Varubi) is a moderate CYP2D6 inhibitor and should not be used with narrow therapeutic index drugs metabolized via CYP2D6. Concomitant use of rolapitant with chronic administration of a strong CYP3A4 inducer (e.g., rifampin) is not recommended due to potential reduced efficacy of rolapitant. Increased concentrations of Breast-Cancer-Resistance Protein (BCRP) substrates (e.g., methotrexate, topotecan), CYP2D6 substrates, or P-gp substrates (e.g., digoxin) may

result in potential adverse reactions. Monitor for adverse reactions if concomitant use cannot be avoided.

5-HT₃ receptor antagonists

Dolasetron (Anzemet), granisetron (generics, Sancuso, Sustol), palonosetron (Aloxi), and ondansetron (Zofran, Zuplenz) are metabolized by various CYP450 enzymes; however, due to the variety of enzymes involved, clinically significant drug interactions are limited.

In patients treated with potent inducers of CYP3A4 (e.g., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased, and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

Granisetron is metabolized by CYP1A1 and CYP3A4 enzymes of the hepatic cytochrome P-450 system. Inducers or inhibitors of these enzymes can affect the clearance and/or half-life of this drug. Granisetron, itself, is neither an inducer nor inhibitor of the P-450 system.

The concomitant use of ondansetron and tramadol may decrease the analgesic effectiveness of tramadol.

Blood levels of hydrodolasetron increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of CYP450) for 7 days and decreased 28% with coadministration of rifampin (potent inducer of CYP450) for 7 days. Blood levels of hydrodolasetron decreased approximately 27% when IV dolasetron was administered with atenolol. Caution should be exercised when dolasetron is coadministered with drugs that prolong ECG intervals and/or cause hypokalemia or hypomagnesemia including those used in chemotherapy and surgery.

QT prolongation has been reported with some formulations of granisetron, as well as ondansetron. The use of granisetron or ondansetron in patients concurrently treated with drugs known to prolong the QT interval and/or is arrhythmogenic may result in clinical consequences. In a double-blind pharmacodynamic study of granisetron-extended release injection (Sustol), no significant effect on QT was seen. However, in a study of 142 cancer patients, 1 patient did have a corrected QT > 500 msec while 4 experienced a change from baseline of > 60 msec.

Combination Products

Fosnetupitant/palonosetron (Akynzeo) and netupitant/palonosetron (Akynzeo) contain netupitant (or its prodrug), a moderate inhibitor of cytochrome CYP3A4. These agents should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4 because the plasma concentrations of the medication can increase. Netupitant is also mainly metabolized by CYP3A4. Avoid concomitant use of netupitant/palonosetron in patients who are chronically using a strong CYP3A4 inducer (e.g., rifampin, carbamazepine, phenytoin). A strong CYP3A4 inducer can decrease the efficacy of fosnetupitant/palonosetron or netupitant/palonosetron by substantially reducing plasma concentrations of the netupitant component. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, diltiazem, clarithromycin, ritonavir, nelfinavir) can significantly increase the systemic exposure to the netupitant component of fosnetupitant/palonosetron and netupitant/palonosetron, but no dosage adjustment is necessary.

A 2-fold increase in the systemic exposure of dexamethasone was observed 4 days after a single dose of netupitant or fosnetupitant, and the duration of the effect was not studied beyond 4 days.

Administer a reduced dose of dexamethasone with fosnetupitant/palonosetron and netupitant/palonosetron.

When administered with netupitant, the systemic exposure to midazolam was significantly increased. Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (e.g., alprazolam, triazolam) when administering these drugs with fosnetupitant/palonosetron or netupitant/palonosetron.

Serotonin syndrome has been described following the concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors.

Cannabinoids

Both of the cannabinoids, dronabinol (Marinol, Syndros) and nabilone (Cesamet), are highly protein bound and may displace other highly protein bound drugs. Examples include tricyclic antidepressants, amphetamines, barbiturates, benzodiazepines, fluoxetine, theophylline, and others. A change in dosage of the concomitant drug may be necessary. Consult prescribing information for dosage recommendations.

Dronabinol and nabilone should be used with caution when used concomitantly with sedatives, hypnotics, or other psychoactive medications due to the potential for synergistic CNS effects.

Dronabinol oral solution (Syndros) can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction. Avoid concomitant use with products that contain disulfiram and / or metronidazole; they should be discontinued at least 14 days before or 7 days after Syndros treatment.

Nabilone should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances because these substances can potentiate its central nervous system effects.

Antidopaminergics

Anticholinergic drugs and narcotic analgesics antagonize the effects of metoclopramide (Reglan, Metozolv ODT) on gastrointestinal motility. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

Metoclopramide has been shown to release catecholamines in patients with essential hypertension. It is suggested that it should be used cautiously, if at all, in patients taking monoamine oxidase (MAO) inhibitors.

Metoclopramide is a central dopamine antagonist and may affect the actions of dopamine agonists and COMT inhibitors.

Metoclopramide should not be used with other medications known to cause extrapyramidal reactions, such as antidepressant, antipsychotic, and neuroleptic agents.

Absorption of drugs from the stomach may be diminished by metoclopramide (e.g., digoxin), whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption; therefore, insulin dosage or timing of dosage may require adjustment.

Antihistamines

Doxylamine/pyridoxine (Diclegis, Bonjesta) may enhance the toxic effects of CNS depressants and anticholinergics. Doxylamine/pyridoxine is contraindicated in concomitant use with MAO inhibitors due to an intensification and prolongation of CNS effects. There are no known drug interactions with the vitamin B6 component of doxylamine/pyridoxine. False positives on urine drug screening have been reported with doxylamine/pyridoxine; results should be confirmed.

Others (phosphorated carbohydrate solution [Emetrol OTC] and trimethobenzamide [Tigan])

Phosphorated carbohydrate, due to its high phosphate content, could lead to higher phosphorus levels in patients at risk or on concomitant medications that could also increase this risk. Likewise, it should not be used in patients who require phosphorus-lowering therapy, as it could counteract these effects. Phosphate may bind select salts and minerals (e.g., magnesium, iron, zinc, copper). Phosphate salts can acidify the urine, potentially leading to increased salicylate levels if used concomitantly with a salicylate product.

Trimethobenzamide should not be used with other agents that may cause CNS depression (including alcohol) or extrapyramidal symptoms. If concomitant use cannot be avoided, close monitoring is recommended.

ADVERSE EFFECTS^{153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177}

Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
NK₁ receptor antagonist								
aprepitant (Emend)*	3–6	> 0.5	5–13.2	nr	0.5–5.7	6–10.3	4.7–17.8	5.8–12.7
aprepitant injectable emulsion (Cinvanti)	nr	nr	3	< 1	nr	nr	2	< 1
fosaprepitant (Emend for injection)	1.1–2.8	nr	2.2	< 1	nr	1.1	1.4–2.9	< 1
rolapitant (Varubi)	nr	nr	nr	nr	nr	nr	nr	nr
5-HT₃ antagonists								
dolasetron (Anzemet)	< 1	2.2–3	7–22.9	nr	< 2–5.3	2.1–5.3	2.6–5.7	nr
granisetron	5–6 (oral) 2.8–5.6 (IV)	nr (oral) nr (IV)	14–21 (oral) 8.6–14 (IV)	nr (oral) nr (IV)	reported (oral) reported (IV)	4–9 (oral) 3.4 (IV)	nr (oral) nr (IV)	20
granisetron injection, extended-release (Sustol)	< 3	nr	9–13	nr	nr	8–9	11–21	nr
granisetron transdermal (Sancuso)†	reported	nr	< 1	nr	reported	reported [†]	nr	reported
ondansetron (Zofran, Zuplenz)	1–2 (oral) 5 (IV)	reported (oral and IV)	11–27 (oral) 17 (IV)	nr (oral and IV)	5 (oral) reported (IV)	3–7 (oral) 16 (IV)	9–13 (oral) nr (IV)	nr (oral and IV)
palonosetron (Aloxi)	< 1	1	9	< 1	1	1	< 1	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Nr = not reported.

* Data reported for both oral capsules and suspension.

† Constipation is the predominant adverse effect associated with granisetron transdermal (Sancuso), occurring at a rate of 5.4%.

Adverse Effects (continued)

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
Combination Products								
fosnetupitant/palonosetron (Akynzeo)*; netupitant/palonosetron (Akynzeo)	< 1	nr	9	nr	nr	nr	7	nr
Cannabinoids								
dronabinol (Marinol, Syndros)	< 1	> 1	< 1	3–10	< 1	< 1	reported	3–10
nabilone (Cesamet)	nr	reported	6–7	11–38	8	reported	reported	4
Antidopaminergics								
metoclopramide (Metozolv ODT)	reported	reported	5.2	nr	reported	reported	2.1	4.2
metoclopramide (Reglan)	reported	reported	reported	nr	reported	reported	10	reported
Antihistamines								
doxylamine/ pyridoxine (Diclegis, Bonjesta)†	nr	nr	nr	nr	nr	nr	nr	nr
Other								
trimethobenzamide (Tigan)	nr	nr	reported	nr	reported	reported	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Nr = not reported.

*Adverse effects reported in the labeling for injectable fosnetupitant/palonosetron (Akynzeo) were described as generally similar to those reported with the oral formulation of netupitant/palonosetron (Akynzeo).

† Doxylamine/ pyridoxine (Diclegis, Bonjesta): The most common adverse effect occurring in ≥ 5% of patients reported was somnolence (14.3%). In post marketing, adverse effects that occurred include dyspnea, palpitations, tachycardia, vertigo, visual disturbances, abdominal distension, anxiety, dysuria, and rash. Frequency could not be accurately determined since these are reported voluntarily.

SPECIAL POPULATIONS^{178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202}

Pediatrics

Prescribing information states that oral ondansetron (Zofran) can be used for patients older than 4 years old. However, little information is available about oral ondansetron dosing in pediatric patients 4 years of age or younger. There is no experience with the use of oral ondansetron in the prevention of radiation-induced or post-operative N/V in pediatric patients.

Information is lacking regarding the use of injectable ondansetron (Zofran) in surgical patients younger than 1 month of age and use in cancer patients younger than 6 months of age. The safety and effectiveness of ondansetron soluble film (Zuplenz) has been established for the prevention of N/V associated with moderately emetogenic chemotherapy in patients 4 years of age and older. Otherwise, the safety and effectiveness of this product in children have not been evaluated.

Dolasetron (Anzemet) tablets are indicated for use in patients 2 years of age and older in the prevention of post-operative N/V and the prevention of chemotherapy-induced N/V.

Safety and efficacy of oral granisetron and granisetron transdermal (Sancuso) have not been established for pediatric patients. Granisetron injectable may be used for chemotherapy-induced N/V in pediatric patients 2 to 16 years of age. Granisetron may be effective in patients older than 4 years old, according to limited randomized, controlled trials for post-operative N/V.^{203,204,205} There is no experience with oral granisetron in the prevention of radiation-induced N/V in pediatric patients. Safety and effectiveness of palonosetron capsules (Aloxi) in patients less than the age of 18 years have not been established; however use of intravenous palonosetron (Aloxi) is indicated in patients as young as 1 month for the prevention of N/V associated with cancer chemotherapy.

Aprepitant (Emend) capsules are approved for prevention of N/V secondary to moderately and highly emetogenic chemotherapy in patients 12 years of age and older. Likewise, aprepitant (Emend) oral suspension is approved for prevention of N/V secondary to moderately and highly emetogenic chemotherapy in patients 6 months of age and older weighing ≥ 6 kg. However, neither formulation is approved in pediatrics for the prevention of post-operative N/V. Fosaprepitant (Emend for injection) is approved for use in pediatric patients as young as 6 months of age for the prevention of acute and delayed N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin, and prevention of delayed N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Aprepitant injectable emulsion (Cinvanti) and rolapitant (Varubi) have not been studied in patients less than 18 years old.

The safety and effectiveness of fosnetupitant/palonosetron (Akynzeo), netupitant/palonosetron (Akynzeo), and granisetron extended-release injection (Sustol) in pediatric patients has not been established.

Neither dronabinol (Marinol, Syndros) nor nabilone (Cesamet) have been studied in children. Caution is recommended in prescribing dronabinol or nabilone for children because of the psychoactive effects

Safety and effectiveness of oral metoclopramide (Reglan, Metozolv ODT) in pediatric patients have not been established. Metoclopramide injectable (Reglan) is used in pediatric patients to facilitate small bowel intubation.

Trimethobenzamide (Tigan) injection is contraindicated in pediatric patients.

The safety and efficacy of doxylamine/pyridoxine (Diclegis, Bonjesta) has not been established in pediatric patients.

Pregnancy

Doxylamine/pyridoxine (Diclegis, Bonjesta) are intended for use in pregnant women. In a meta-analysis, there have been no significant relationship between fetal abnormalities and use in the first trimester, for the combination of doxylamine/pyridoxine, with or without dicyclomine. In epidemiologic studies, there are no reports of increased congenital malformations risks with doxylamine/pyridoxine (Bonjesta, Diclegis).

The 5-HT₃ antagonists, ondansetron (Zuplenz), granisetron (generic, Sancuso), dolasetron (Anzemet), and palonosetron (Aloxi) are Pregnancy Category B. Ondansetron (Zofran), aprepitant (Emend), and fosaprepitant (Emend for injection) were previously assigned Pregnancy Category B, but their labeling has been updated to reflect the Pregnancy and Lactation Labeling Final Rule (PLLR). Available data do not provide an association of ondansetron and adverse fetal outcomes, and animal studies do not suggest fetal harm. Data are insufficient to inform of a drug associated risk with aprepitant and fosaprepitant. This description also applies to aprepitant injectable emulsion (Cinvanti), although it was never assigned a Pregnancy Category. Trimethobenzamide (Tigan capsules) was previously assigned Pregnancy Category C, but its labeling has been updated to reflect the Pregnancy and Lactation Labeling Final Rule (PLLR); data are insufficient to inform of a drug associated risk. Likewise, there are no or limited available data on the use of granisetron extended-release injection (Sustol) or rolapitant (Varubi) in pregnant women; data on their use during pregnancy are insufficient to inform prescribers of the drug-associated risk. Nabilone (Cesamet) is Pregnancy Category C. Dronabinol (Marinol, Syndros) should not be used in pregnant women; although published data are limited on the use of synthetic cannabinoids during pregnancy, use of cannabis during pregnancy have been associated with adverse fetal/neonatal outcomes. Previously, netupitant/palonosetron (Akynzeo) was Pregnancy Category C, but with the approval of fosnetupitant/palonosetron (Akynzeo), the labeling was updated in compliance with the PLLR; limited available data with use of these products in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.

Metoclopramide oral disintegrating tablets (Metozolv ODT) is Pregnancy Category B. The labeling for metoclopramide tablets (Reglan) has been updated to comply with the PLLR. No increased risk of adverse pregnancy-related outcomes with use of metoclopramide during pregnancy has been identified with metoclopramide tablets (Reglan); however, metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery.

Trimethobenzamide (Tigan injection) is Pregnancy Category C.

Geriatrics

Dronabinol (Marinol, Syndros) and nabilone (Cesamet) should be used with caution in elderly patients because they may be more sensitive to its neurological, psychoactive, and postural hypotensive effects. Dose selection should be initiated at the low end of the dosing range. Patients with dementia are at an increased risk for falls due to the underlying disease state and should be monitored closely and placed on falls precautions prior to initiation of therapy.

DOSAGES^{206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230}

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK₁ receptor antagonists						
aprepitant (Emend)	125 mg 1 hour prior to chemotherapy day 1, then 80 mg once daily in the morning on days 2 and 3 as part of regimen including corticosteroid and a 5-HT ₃ antagonist (suspension may be used for those unable to use capsules)	Capsules (≥ 12 years old): dosing is the same as for adults Suspension (patients ≥ 6 months and ≥ 6 kg): 3 mg/kg (maximum 125 mg) 1 hour prior to chemotherapy day 1, then 2 mg/kg (maximum 80 mg) once daily in the morning on days 2 and 3 as part of regimen including corticosteroid and a 5-HT ₃ antagonist	--	40 mg within 3 hours prior to induction of anesthesia	--	capsules: 40 mg, 80 mg, 125 mg bi-fold pack: two 80 mg capsules tri-fold/tripack pack: one 125 mg capsule and two 80 mg capsules oral suspension: 125 mg packaged with oral dosing dispensers and a mixing cup (brand Emend only)

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK₁ receptor antagonists						
aprepitant (Cinvanti)	<p>Single dose regimen for highly emetogenic chemotherapy (HEC): 130 mg on day 1 of a 4 day regimen as an IV infusion over 30 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid and a 5-HT₃ antagonist</p> <p>Regimen for moderately emetogenic chemotherapy (MEC): 100 mg on day 1 of a 3 day regimen as an IV infusion over 30 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid and a 5-HT₃ antagonist (with oral aprepitant used on days 2 and 3)</p>	--	--	--	--	Injectable emulsion: 130 mg/18 mL in a single-dose vial

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK₁ receptor antagonists						
fosaprepitant (Emend for injection)	Single dose regimen for highly emetogenic chemotherapy (HEC): 150 mg on day 1 of a 4 day regimen as an infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid (days 1-4) and a 5-HT ₃ antagonist (day 1) Single dose regimen for moderately emetogenic chemotherapy (MEC): 150 mg on day 1 as an infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid and a 5-HT ₃ antagonist	--	--	--	--	injection: 150 mg per single-use vial

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK₁ receptor antagonists (continued)						
rolapitant (Varubi)*	Administer prior to the initiation of each cycle of chemotherapy without regard to food, but at no less than 2 week intervals; Rolapitant is to be used in combination with a 5-HT ₃ receptor antagonist and dexamethasone HEC: 180 mg (2 tablets) orally or 166.5 mg IV over 30 minutes administered 2 hours prior to chemotherapy on day 1 with a corticosteroid and a 5-HT ₃ antagonist (corticosteroid also administered days 2-4) MEC: 180 mg (2 tablets) orally or 166.5 mg IV over 30 minutes administered 2 hours prior to chemotherapy on day 1 with a corticosteroid and a 5-HT ₃ antagonist (5-HT ₃ antagonist administered per prescribing information)	--	--	--	--	tablets: 90 mg

* Rolapitant (Varubi) injectable emulsion (166.5 mg/92.5 mL) is obsolete; final expiry was September 30, 2018.

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT₃ antagonists						
dolasetron (Anzemet)	100 mg orally within 1 hour before chemotherapy	2 to 16 years: 1.8 mg/kg (up to 100 mg) orally within 1 hour before chemotherapy	--	100 mg orally within 2 hours before surgery	2 to 16 years: 1.2 mg/kg orally (up to 100 mg) given within 2 hours before surgery	tablets: 50 mg, 100 mg
granisetron	Oral: 2 mg up to 1 hour before chemotherapy for 1 dose OR 1 mg up to 1 hour before chemotherapy followed by 1 mg 12 hours after the first dose Injectable: 10 mcg/kg IV given up to 30 minutes before initiation of chemotherapy only on the day(s) chemotherapy is given	Injectable (2 to 16 years): 10 mcg/kg	2 mg once daily taken within 1 hour of radiation	Injectable: Prevention: 1 mg IV over 30 seconds before induction or immediately before reversal of anesthesia. Treatment: 1 mg IV over 30 seconds	--	tablets: 1 mg injection: 0.1 mg/1 mL, 1 mg/1 mL, 4 mg/4 mL

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT₃ antagonists (continued)						
granisetron injection, extended-release (Sustol)	10 mg as a single subcutaneous (SC) injection 30 minutes prior to the emetogenic chemotherapy, on day 1, by a healthcare professional; administer in combination with dexamethasone Due to the viscosity of the solution, injection should be administered over 20 to 30 seconds Do not administer more frequently than once every 7 days (effects last for ≈ 5 days); use > 6 months is not recommended Do not administer more frequently than once every 14 days in patients with moderate renal impairment (creatinine clearance [CrCl] 30-59 mL/min); avoid in patients with severe impairment (CrCl < 30 mL/min)	--	--	--	--	injection: 10 mg/0.4 mL extended-release injection in a single-dose, pre-filled syringe
granisetron transdermal (Sancuso)	Apply single patch to upper outer arm 24 hours prior to chemotherapy; remove 24 hours after completion of chemotherapy The patch can be worn for up to 7 days	--	--	--	--	transdermal patch containing 34.3 mg granisetron that releases 3.1 mg over 24 hours for 7 days

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT₃ antagonists (continued)						
ondansetron (Zofran, Zuplenz)	<p>HEC: 24 mg (three 8 mg tabs) given 30 minutes before start of chemotherapy;</p> <p>MEC: 8 mg given 30 minutes before start of chemotherapy with a subsequent dose 8 hours after the first dose; 8 mg should then be given every 12 hours for 1 to 2 days following completion of chemotherapy</p> <p>Injection: 0.15 mg/kg IV for 3 doses up to a maximum of 16 mg per dose</p> <p>The first dose is infused over 15 minutes starting 30 minutes before the start of chemotherapy; subsequent doses (0.15 mg/kg up to 16 mg per dose) are administered 4 and 8 hours after the first dose</p>	<p>HEC: No experience with 24 mg dosage</p> <p>MEC: 4-11 years: 4 mg given 30 minutes before chemotherapy with subsequent doses 4 and 8 hours after the first dose; 4 mg should be given every 8 hours for 1 to 2 days after completion of chemotherapy</p> <p>≥ 12 years: same as adult.</p> <p>Injection: 6 months – 18 years: 0.15 mg/kg IV for 3 doses up to a maximum of 16 mg per dose; the first dose is given 30 minutes prior to moderately to HEC</p> <p>Subsequent doses (0.15 mg/kg IV up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose (infused over 15 minutes)</p>	8 mg up to 2 hours before radiation and up to 3 times daily for 1 to 2 days	16 mg (two 8mg tabs) 1 hour before induction of anesthesia	<p>1 month to 12 years:</p> <p><40 kg: 0.1 mg/kg IV over 2 to 5 minutes</p> <p>> 40 kg: 4 mg IV over 2 to 5 minutes</p> <p>immediately prior to or following anesthesia induction or post-operatively if the patient did not receive prophylactic antiemetics and has N/V within 2 hours after surgery</p>	<p>tablets: 4 mg, 8 mg</p> <p>oral soluble film (Zuplenz): 4 mg, 8 mg</p> <p>oral solution: 4 mg/5 mL</p> <p>orally disintegrating tablets (ODT): 4 mg, 8 mg</p> <p>injection: 2 mg/mL in 2 mL single-use vials or ampules (generic only) and 20 mL multi-dose vials</p> <p>prefilled syringe: 2 mg/1 mL in syringes containing 2 mL solution for injection: 16 mg per 50 mL or 100 mL in 0.9% sodium chloride (generic only)</p>

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT₃ antagonists (continued)						
palonosetron (Aloxi)	A single 0.25 mg IV dose administered over 30 seconds Dosing should occur approximately 30 minutes prior to start of chemotherapy	--	--	A single 0.075 mg IV dose administered over 10 seconds immediately prior to the induction of anesthesia	--	injection: 0.25 mg/2 mL (generic only), 0.25 mg/5 mL single-use vials
Combination products						
fosnetupitant/palonosetron (Akynzeo)	1 vial (235 mg/0.25 mg) reconstituted in 50 mL (prepared as described in labeling) and administered as a 30-minute IV infusion approximately 30 minutes prior to the start of chemotherapy	--	--	--	--	injection: 235 mg fosnetupitant/0.25 mg palonosetron (as lyophilized powder for reconstitution) in single-dose vials
netupitant/palonosetron (Akynzeo)	One 300/0.5 mg capsule administered approximately 1 hour prior to the start of chemotherapy as part of a regimen including dexamethasone	--	--	--	--	capsules: 300 mg netupitant/0.5 mg palonosetron

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Cannabinoids						
dronabinol (Marinol)	<p>Capsules (Marinol): Anorexia in adult patients with AIDS – initial dose is 2.5 mg twice daily, 1 hour before lunch and dinner; the dosage can be reduced to 2.5 mg/day administered as a single dose of in the evening at bedtime; the dosage may be gradually increased to a maximum dose of 20 mg/day</p> <p>Chemotherapy-induced nausea and vomiting (CINV) – initial dose of 5 mg/m² given 1 to 3 hours prior to chemotherapy, then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day; the initial starting dose may be adjusted in increments of 2.5 mg/m² if necessary up to a maximum of 15 mg/m² (per dose)</p>	--	--	--	--	capsules: 2.5 mg, 5 mg, 10 mg

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Cannabinoids (continued)						
dronabinol (Syndros)	Anorexia in adult patients with AIDS – initial dose is 2.1 mg twice daily, 1 hour before lunch and dinner; maximum dose is 8.4 mg twice daily CINV – initial dose is 4.2 mg/m ² , 1 to 3 hours prior to chemotherapy, then every 2 to 4 hours after chemotherapy up to 4 to 6 doses per day; give first dose on an empty stomach; doses that follow can be given regardless of meals; however, dosing in relation to meal times should be kept consistent for each chemotherapy cycle (maximum dose is 12.6 mg/m ²) (can be administered via select silicone feeding tubes; see labeling for details)	--	--	--	--	solution (Syndros): 5 mg/mL
nabilone (Cesamet)	Usual adult dose is 1 to 2 mg twice daily; 1 or 2 mg may be given the night prior to chemotherapy or 1 to 3 hours before initial chemotherapy; maximum daily dose of 6 mg in divided doses (3 times a day); the medication may be administered 2 or 3 times a day during the entire course of each chemotherapy cycle and for 48 hours after the last dose of each chemotherapy cycle	--	--	--	--	capsules: 1 mg

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Antidopaminergic Agents						
metoclopramide (Metozolv ODT, Reglan)	1 to 2 mg/kg IV 30 minutes before chemotherapy and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses	--	Relief of symptomatic GERD: 10 mg to 15 mg orally up to 4 times daily at least 30 minutes prior to eating and at bedtime for up to 12 weeks Relief of symptoms associated with diabetic gastroparesis: 10 mg IV, IM or orally 4 times daily at least 30 minutes prior to eating and at bedtime for 2 to 8 weeks; therapy should not exceed 12 weeks Facilitation of intestinal intubation or as a diagnostic aid in gastrointestinal radiography- 10 mg IV in a single dose	10 mg to 20 mg IM or IV near the end of surgery. Repeat every 4 to 6 hours as necessary; if required, a 20 mg dose may be used	--	tablets: 5 mg, 10 mg orally disintegrating tablets: 5 mg, 10 mg (generic only) solution: 5 mg/5 mL (generic only) injection: 5 mg/mL in 2 mL single-use vials or syringes (generic only)

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Antihistamines						
doxylamine/ pyridoxine (Diclegis)	--	--	Nausea and vomiting of pregnancy: initially, take 2 tablets orally at bedtime; if symptoms persist, take an additional tablet in the morning on day 3; if symptoms persist, take an additional tablet mid afternoon on day 4 (maximum dose 4 tablets per day)	--	--	Delayed-release tablets: 10 mg doxylamine/10 mg pyridoxine
doxylamine/ pyridoxine (Bonjesta)	--	--	Nausea and vomiting of pregnancy: initially (day 1), take 1 tablet orally at bedtime; on day 2 if symptoms persist, take an additional tablet in the morning (maximum dose 2 tablets per day)	--	--	Extended-release tablets: 20 mg doxylamine/20 mg pyridoxine

Dosages (continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Others						
phosphorated carbohydrate solution (Emetrol OTC)	--	--	Relief of upset stomach associated with nausea: ages 2 to < 12 years: 1 to 2 teaspoons age > 12 years: 1 to 2 tablespoons May repeat dose every 15 minutes or until distress subsides; should not be taken for more than 1 hour (5 doses)	--	--	oral solution: 3.74 g total sugar + 21.5 mg phosphoric acid per 5 mL
trimethobenzamide (Tigan)	--	--	Nausea and vomiting - 250 or 300 mg capsule: 3 to 4 times daily or 200mg IM 3 to 4 times daily The suppository formulation has not been proven effective for nausea and vomiting	--	--	injection: 100 mg/mL in 2 mL single-use vials and 20 mL multi-dose vials (Tigan only) capsules: 300 mg

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

A number of clinical trials have evaluated ondansetron compared to other antiemetic agents. None of these trials have involved the use of the oral film used as the delivery mechanism in Zuplenz. While no clinical trials have been undertaken to evaluate Zuplenz, this product has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron.

Approval of aprepitant injectable emulsion (Cinvanti) was based on studies utilizing single doses of IV fosaprepitant and oral aprepitant in CINV associated with HEC and MEC.²³¹

Approval of dronabinol (Syndros) was based on studies utilizing dronabinol capsule formulation for both approved indications and pharmacokinetics data.

Results from a bioequivalence trial demonstrated comparability of the IV and oral formulations of rolapitant.^{232, 233}

There have been no safety and efficacy trials conducted with the formulation and strength of doxylamine/pyridoxine (Bonjesta).²³⁴

Chemotherapy-Induced Nausea and Vomiting (CINV)

aprepitant (Emend) plus standard of care versus placebo plus standard of care

Patients receiving cisplatin were blindly assigned to receive 1 of the following 3 regimens: (1) aprepitant 375 mg 1 hour before cisplatin on day 1 and aprepitant 250 mg on days 2 through 5 (n=35); (2) aprepitant 125 mg before cisplatin and aprepitant 80 mg on days 2 through 5 (n=81); or (3) placebo before cisplatin on days 2 through 5 (n=86).²³⁵ All groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin, and dexamethasone 8 mg on days 2 through 5. The primary endpoint was complete response (CR; no emesis and no rescue therapy) over 5 days following cisplatin in up to 6 cycles. The aprepitant 375/250 mg regimen was discontinued early in light of new pharmacokinetic data. In the first cycle, 64% of patients in the aprepitant group and 49% in the standard therapy group had a CR (p<0.05). Thereafter, CR rates for the aprepitant group were still 59% by cycle 6, but decreased to 34% by cycle 6 for the standard therapy group (p<0.05).

A randomized, double-blind, placebo controlled, cross over designed trial was conducted to compare aprepitant versus a placebo.²³⁶ Patients were randomized to receive aprepitant 125 mg on day 3 and 80 mg once per day on days 4 through 7 or placebo in addition to a commercially available 5HT₃ receptor antagonist on days 1 through 5 and dexamethasone on days 1 and 2. The cross over design allowed patients to serve as their own control. The primary endpoint of the study was CR defined as no emetic episodes with no use of rescue medication, of acute (days 1 through 5), and delayed (days 6 through 8) chemotherapy-induced nausea and vomiting (CINV). Secondary endpoints included emetic episodes, use of rescue medication, nausea measurement based on a visual analogue scale (VAS), and patient stated preference after second cycle. Seventy-one patients 15 years of age and older with germ cell tumors receiving a standard 5 day cisplatin regimen were enrolled. Of these patients, 60 completed the study and were available for analysis. Twenty-five (42%) of the patients achieved CR with aprepitant while 8 (13%) achieved CR in the placebo group ($p < 0.001$) during days 1 through 8. Of the 25 patients that received CR with aprepitant, 7 received CR when they crossed over to the placebo arm and of the 8 patients that received CR on placebo, 7 received CR when they crossed over to aprepitant. Twenty-eight (47%) of the patients in the aprepitant group achieved a CR in the acute phase compared with 9 (15%) in the placebo group ($p < 0.001$). Thirty-eight patients (63%) in the aprepitant group achieved a CR in the delayed phase compared to 21 (42%) of the patients in the placebo group ($p < 0.001$).

aprepitant (Emend) versus dexamethasone

A randomized, double-blind, multicenter study was performed in 580 chemotherapy-naive patients with breast cancer treated with anthracyclines plus cyclophosphamide to assess the efficacy of aprepitant and dexamethasone in delayed CINV.²³⁷ Before chemotherapy, all patients were treated with IV 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. The primary end point was rate of CR (no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. Both day 1 (87.6% for dexamethasone and 84.9% for aprepitant [$p < 0.39$]) and days 2 through 5 (79.5% for dexamethasone and 79.5% for aprepitant [$p < 1$]) CR rates were similar and did not reach statistical significance.

aprepitant (Emend) versus placebo in pediatric patients

A phase 3, multicenter, randomized, double-blind study compared the efficacy aprepitant to placebo (both with standard therapy) in patients ages 6 months to 17 years scheduled to receive moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) ($n = 307$).²³⁸ Patients were assigned to aprepitant (3 mg/kg to a maximum of 125 mg) plus ondansetron on day 1 and aprepitant (2 mg/kg to a maximum of 80 mg) on days 2 and 3 or placebo plus ondansetron on day 1 and placebo on days 2 and 3. All doses were weight-based (using either aprepitant oral capsules or aprepitant oral suspension). The primary efficacy endpoint was the proportion of patients who achieved CR (defined as no vomiting, retching, or use of rescue medication) during the delayed phase (25 to 120 hours) after chemotherapy initiation. Fifty one percent (77/152) of patients in the aprepitant group compared to 26% (39/150) in the placebo/control group achieved a CR ($p < 0.0001$).

dolasetron (Anzemet) versus ondansetron (Zofran)

A multicenter, randomized, double-blind study was designed to compare the antiemetic efficacy and safety of single oral doses of dolasetron with a multiple-dose regimen of oral ondansetron in 399

cancer patients receiving MEC.²³⁹ Single oral doses of 25, 50, 100, or 200 mg of dolasetron were administered 1 hour prior to the initiation of chemotherapy. Ondansetron 8 mg, or matching placebo for patients randomized to dolasetron, was given 1.5 hours before and 6.5, 14.5, and 22.5 hours after the start of chemotherapy. A statistically significant ($p < 0.001$) linear dose-response relationship was observed over the entire dolasetron dosage range for all efficacy parameters. CR rates were 45%, 49.4%, 60.5%, and 76.3% for 25 mg, 50 mg, 100 mg, and 200 mg dolasetron, respectively, and 72.3% for ondansetron patients. Overall, there were no significant differences in the incidence of adverse events between any of the dolasetron doses, or between dolasetron and ondansetron; headache was most frequently reported (approximately 15% for each drug). In the study, a single oral 200 mg dolasetron dose was therapeutically equivalent to multiple-dose ondansetron in the prevention of N/V following MEC.

dronabinol (Marinol), ondansetron (Zofran), combination therapy versus placebo

A 5-day, double-blind, placebo-controlled study was conducted in 64 patients to compare the efficacy and tolerability of dronabinol, ondansetron, or the combination for delayed CINV.²⁴⁰ Patients receiving moderately to highly emetogenic chemotherapy were given dexamethasone 20 mg orally, ondansetron 16 mg IV, and either placebo or dronabinol 2.5 mg pre-chemotherapy on day 1. Patients randomized to active treatment (dronabinol and/or ondansetron) also received dronabinol 2.5 mg after chemotherapy on day 1. On day 2, fixed doses of placebo, dronabinol 10 mg, ondansetron 16 mg, or combination therapy were administered. On days 3 to 5, patients received placebo, flexible doses of dronabinol 10 to 20 mg, ondansetron 8 to 16 mg, or dronabinol 10 to 20 mg and ondansetron 8 to 16 mg. The primary outcome was a total response (TR) of nausea intensity < 5 mm on visual analog scale, no vomiting/retching and no use of rescue antiemetic. The TR was similar for the active treatments: dronabinol (54%), ondansetron (58%), and combination (47%) versus placebo (20%). Nausea absence was significantly greater for the active treatment groups versus placebo (15%): dronabinol (71%), ondansetron (64%), and combination (53%; $p < 0.05$ for all). Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Dronabinol or ondansetron were similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. All active treatments were well tolerated. The population size is the greatest limitation of these data.

fosaprepitant (Emend for injection) versus placebo (control regimen)

An international, multicenter, phase 3, double-blind, parallel-group, randomized trial compared fosaprepitant to placebo with a background control regimen in adult cancer patients undergoing MEC ($n = 1,015$).²⁴¹ Patients were randomized 1:1 to either fosaprepitant 150 mg IV or placebo on day 1 with background ondansetron and dexamethasone on day 1 and ondansetron on days 2 and 3. The primary efficacy endpoint was the proportion of patients achieving CR (no vomiting, no rescue medication) during the delayed phase (25 to 120 hours following MEC initiation). Safety measures and CR during the overall (0 to 120 hours) and acute (0 to 24 hours) phases were also measured. During the delayed phase, fosaprepitant achieved CR in 78.9% of the patients compared to 68.5% in the placebo group ($p < 0.001$). Fosaprepitant was also superior to placebo regarding CR in the overall phase (77.1% versus 66.9%, respectively; $p < 0.001$) but not in the acute phase (93.2% versus 91%, respectively; $p = 0.184$). Adverse effects were comparable between treatment groups; fatigue, diarrhea, and constipation were the most commonly reported adverse effects in both groups.

fosnetupitant/palonosetron (Akyzreo) versus netupitant/palonosetron (Akyzreo)

A multinational, phase 3, randomized, double-blind study in chemotherapy-naïve patients with solid tumors assessed the safety of a single dose of IV fosnetupitant/palonosetron over 30 minutes before initial and repeated cycles of HEC (n=404 [1,312 cycles]).²⁴² In the study, patients were randomized to either IV fosnetupitant/palonosetron or oral netupitant/palonosetron, both administered with oral dexamethasone on days 1 through 4. Overall, the types of adverse events and incidence (12.8% with the IV formulation and 11.4% with the oral formulation) were similar between groups. The most common adverse effect reported was constipation (6.4% with the IV formulation and 6% with the oral formulation). No serious adverse events were reported in either group, and no infusion site reactions occurred with the IV formulation.

granisetron versus granisetron transdermal (Sancuso)

A phase 3, randomized, parallel-group, double-dummy, double-blind trial was conducted in 641 patients who received multi-day chemotherapy to compare the efficacy, tolerability, and safety of granisetron transdermal to oral granisetron 2 mg once daily in the prevention of N/V.²⁴³ The primary endpoint was proportion of patients achieving no vomiting and/or retching, no more than mild nausea, and without use of a rescue medication from the first administration until 24 hours after start of the last day's administration of multi-day chemotherapy. The effect of granisetron transdermal was established in 60.2% of patients and in 64.8% of the patients taking granisetron orally (p=NS).

granisetron versus ondansetron (Zofran)

A double-blind study was conducted to determine the efficacy of oral ondansetron, oral granisetron, and IV ondansetron for the prevention/control of N/V associated with high-dose chemotherapy or radiotherapy prior to hematopoietic stem cell transplantation.²⁴⁴ In addition to dexamethasone 10 mg IV, 102 patients were randomized to receive either ondansetron 8 mg orally every 8 hours, granisetron 1 mg orally every 12 hours, or ondansetron 32 mg IV every 24 hours, each given on days 1 and 2. Overall CR rates were 48% for oral ondansetron, 47% for oral granisetron, and 49% for IV ondansetron; this difference is not statistically significant (p=NS). Overall major efficacy rates were 82% for oral ondansetron, 84% for oral granisetron, and 81% for IV ondansetron (p=NS). Mean VAS nausea scores were 32 for oral ondansetron, 32 for oral granisetron, and 27 for IV ondansetron (p=NS).

A double-blind, randomized, crossover study comparing granisetron 3 mg/day and ondansetron 24 mg/day enrolled 309 patients receiving 2 cycles of identical chemotherapy over 5 days.²⁴⁵ Primary efficacy variables were prospectively defined as CR (no vomiting and mild or absent nausea) over 5 days and patient preference. Both agents achieved good control of emetic symptoms with five-day CR rates of 44% on granisetron and 39.8% on ondansetron (p=NS). CR rates were very similar in patients receiving either cisplatin or ifosfamide. There was a statistically significant difference in patient preference in favor of granisetron (p=0.048).

granisetron extended-release (ER) injection (Sustol) versus palonosetron (Aloxi)

A phase 3, randomized, multicenter, double-blind, parallel-group, non-inferiority study (n=733) compared a single 10 mg subcutaneous (SC) dose of granisetron ER (Sustol) to a single 0.25 mg IV dose of palonosetron hydrochloride in cancer patients given MEC or anthracycline and cyclophosphamide (AC) chemotherapy.²⁴⁶ Patients also received oral and IV dexamethasone per treatment protocol. The primary endpoints were percentage of patients with a CR, defined as no emetic episodes (vomit and/or retching) and no use of rescue medication, during the acute phase (0 to 24 hours) and delayed phase (>

24 hours to 120 hours). Non-inferiority (defined as a lower level of difference of 15%) of granisetron ER to palonosetron HCl was demonstrated in the acute and delayed phases of MEC and of AC combination chemotherapy. For MEC, 83% of patients treated with granisetron ER versus 89% with palonosetron demonstrated a CR in the acute phase. Whereas, for the delayed phase, 69% of patients treated with granisetron ER versus 70% with palonosetron achieved CR. For AC therapy, 70% of patients treated with granisetron ER versus 64% with palonosetron demonstrated a CR in the acute phase. For AC therapy, 50% of patients treated with granisetron ER versus 47% with palonosetron was demonstrated in the delayed phase.

netupitant/palonosetron (Akyzreo) versus palonosetron (Aloxi)

A randomized, parallel-group, double-blind, multicenter trial compared a single oral dose of netupitant/palonosetron to a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin.²⁴⁷ The efficacy of netupitant/palonosetron was assessed in 135 patients who received netupitant/palonosetron (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg. Patients in the netupitant/palonosetron group also received dexamethasone 12 mg on day 1 and dexamethasone 8 mg once daily on days 2 through 4. Patients in the palonosetron group received dexamethasone 20 mg on day 1 and dexamethasone 8 mg twice daily on days 2 through 4. The key efficacy endpoints were the percentage of patients with a CR (defined as no emetic episode and no use of rescue medication) for the 25 to 120 hour interval (delayed phase), CR for the 0 to 24 hour interval (acute phase), and CR within 120 hours (overall phase) after the start of the chemotherapy administration. Netupitant/palonosetron had a statistically significant increase in the percentage of patients achieving CR in all 3 phases when compared to palonosetron. The netupitant/palonosetron group had a CR in the delayed phase of 90.4% versus 80.1% ($p=0.032$) in the palonosetron group. The netupitant/palonosetron group had a CR in the acute phase of 98.5% versus 89.7% ($p=0.002$) in the palonosetron group. The netupitant/palonosetron group had a CR in the overall phase of 89.6% versus 76.5% ($p=0.003$) in the palonosetron group.

A randomized, parallel-group, double-blind, multicenter trial was conducted that compared a single oral dose of netupitant/palonosetron to a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide (AC) regimen for the treatment of a solid malignant tumor^{248,249} All patients received a single oral dose of dexamethasone. After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. A total of 1,450 patients (netupitant 300 mg/palonosetron 0.5 mg, $n=725$; palonosetron 0.5 mg $n=725$) received study medication: of these, 1,438 patients (98.8%) completed cycle 1 and 1,286 patients (88.4%) continued treatment in the multiple-cycle extension. The primary efficacy endpoint was the percentage of patients achieving CR in the delayed phase, 25 to 120 hours after the start of chemotherapy administration and the major secondary efficacy endpoints included the percentage of patients achieving CR in the acute and overall phases. Netupitant/palonosetron had a statistically significant increase in the percentage of patients achieving CR in the delayed phase and both secondary endpoints of the percentage of patients achieving CR in the acute phase and overall phase. The netupitant/palonosetron group had a CR in the delayed phase of 76.9% versus 69.5% ($p=0.001$) in the palonosetron group. The netupitant/palonosetron group had a CR in the acute phase of 88.4% versus 85% ($p=0.047$) in the palonosetron group. The netupitant/palonosetron group had a CR in the overall phase of 74.3% versus 66.6% ($p=0.003$) in the palonosetron group.

ondansetron orally disintegrating tablet (Zofran ODT) versus ondansetron conventional tablet formulation (Zofran)

Due to a lack of other available data, this study has been included. The efficacy of ondansetron ODT was compared to the conventional oral tablet of ondansetron in controlling N/V among breast cancer patients receiving high-dose epirubicin.²⁵⁰ In a randomized trial, 134 patients received ondansetron ODT 8 mg twice daily or ondansetron tablet 8 mg twice daily, both for 3 days. Ondansetron tablet was significantly better at controlling emesis (72% versus 52%, respectively; $p=0.02$) and statistically insignificant when attempting to control nausea (66% versus 48%, respectively; $p=0.054$) compared to ondansetron ODT. However, when looking at major control of emesis (as having 0 to 2 emetic episodes during the 3 days) between the conventional ondansetron tablet versus ondansetron ODT, there was no real difference (76% versus 70%, respectively; $p=0.28$). For control of major emesis and nausea, there are no major differences between the formulations.

palonosetron (Aloxi) versus granisetron versus palonosetron plus aprepitant (Emend) versus palonosetron plus dexamethasone

A randomized, double-blind, placebo controlled study was conducted in 1,021 patients to determine the comparative efficacy of four treatment regimens.²⁵¹ Patients at least 18 years of age with a cancer diagnosis scheduled to receive their first treatment with any dose or schedule other than multiple day doses of doxorubicin, epirubicin, cisplatin, carboplatin, or oxaliplatin were included (both high and moderate emetogenic potential). Patients were assigned to either palonosetron 0.25 mg IV plus dexamethasone 20 mg IV plus oral placebo on day 1 with oral prochlorperazine on days 2 and 3 (group 1), granisetron 1 mg IV plus dexamethasone 20 mg IV plus oral placebo day 1 with oral prochlorperazine on days 2 and 3 (group 2), palonosetron 0.25 mg IV plus dexamethasone 12 mg IV plus aprepitant 125 mg orally on day 1 with aprepitant 80 mg orally and dexamethasone 8 mg orally on days 2 and 3 (group 3), and palonosetron 0.25 mg IV plus dexamethasone 20 mg IV plus placebo orally on day 1 with prochlorperazine 10 mg orally and dexamethasone 8 mg orally on days 2 and 3 (group 4). The primary outcome of the study was to determine efficacy through a difference in mean delayed nausea in the following scenarios: palonosetron in comparison to granisetron, palonosetron with or without an additional dose of dexamethasone on day 2 in addition to prochlorperazine, and aprepitant in comparison to prochlorperazine with or without dexamethasone on day 2. Nausea was reported on a home record at 4 time intervals per day (morning, afternoon, evening, and night) and was rated using a 7 point scale. Of the 1,021 patients that were randomly assigned to a group, 944 patients had evaluable data for delayed nausea (DN). In the group 1 to group 2 comparison, palonosetron was not statistically significantly more effective than granisetron with a mean DN difference of -0.013 (95% CI, -0.225 to 0.2; $p=0.718$). In the group 1 to group 4 comparison, the addition of dexamethasone on days 2 and 3 resulted in a more effective treatment with a mean DN difference of 0.195 (95% CI, -0.017 to 0.407; $p=0.01$). In the group 3 to group 4 comparison, aprepitant was not statistically significantly more effective than prochlorperazine in combination with palonosetron and dexamethasone with a mean DN difference of -0.025 (95% CI, -0.236 to 0.186; $p=0.557$).

palonosetron (Aloxi) versus ondansetron, dolasetron, and granisetron

Four randomized, double-blind, phase 3 trials compared palonosetron with ondansetron, dolasetron, and granisetron and results were reported as a pooled analysis of patient level data.²⁵² Two of the trials were conducted in patients scheduled to receive MEC and 2 in patients scheduled to receive HEC. Dosages included in the studies that were analyzed were palonosetron 0.25 mg or 0.75 mg,

ondansetron 32 mg, dolasetron 100 mg, and granisetron 40 µg/kg. Endpoints included CR (no emesis and no rescue antiemetics) in the acute, delayed, and overall post chemotherapy periods, and secondary outcomes of complete control (no emesis, no rescue antiemetics, and no more than mild nausea), number of emetic episodes, and nausea severity. CR rates were significantly higher for palonosetron (n=1,787) versus older 5-HT₃ antagonists (ondansetron, dolasetron, and granisetron) (n=1,175) in the delayed (57% versus 45%; p<0.0001) and overall periods (51% versus 40%; p<0.0001) but not the acute phase (69% versus 66%; p=0.091). Significant differences in secondary outcomes complete control rates and nausea severity were observed for the delayed and overall periods and in emetic episodes for all 3 periods. The incidence of treatment-related adverse events was similar with palonosetron (0.25 mg, 20%; 0.75 mg, 26.5%) and older 5-HT₃ antagonists (27.5%).

rolapitant (Varubi), dexamethasone, and granisetron versus placebo, dexamethasone, and granisetron

Two randomized, double-blind, parallel group studies (Study 1 and Study 2) compared a rolapitant regimen (rolapitant, dexamethasone, and the 5-HT₃ receptor antagonist, granisetron) with control therapy (placebo, dexamethasone, granisetron) in patients receiving chemotherapy including cisplatin > 60 mg/m² (HEC).²⁵³ The primary endpoint in both studies was CR (no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of CINV. In Study 1, a total of 532 patients were randomized to either the rolapitant or control regimens. Patients ranged from 20 to 90 years of age, with a mean age of 57 years. The mean cisplatin dose was 77 mg/m². Eighty-two percent of patients received a concomitant chemotherapy agent in addition to cisplatin with the most common agents being gemcitabine (17%), paclitaxel (12%), fluorouracil (11%) and etoposide (10%). In Study 2, a total of 555 patients were randomized to either the rolapitant or control regimens. Patients ranged from 18 to 83 years of age, with a mean age of 58 years. The mean cisplatin dose was 76 mg/m². Eighty-five percent of patients received a concomitant chemotherapy agent in addition to cisplatin with the most common agents being vinorelbine (16%), gemcitabine (15%), fluorouracil (12%) and etoposide (11%). In both studies, a significantly greater proportion of patients in the rolapitant group had CRs in the delayed phase of nausea and vomiting as compared to patients in the control group (Study 1: 73% versus 58%; Study 2: 70% versus 62%; p<0.001 for both).

A randomized, double-blind, parallel group study compared a rolapitant regimen (rolapitant 180 mg on day 1, dexamethasone, and the 5-HT₃ receptor antagonist granisetron) to control therapy (dexamethasone and granisetron) in patients receiving a MEC regimen that included at least 50% of patients receiving a combination of anthracycline and cyclophosphamide.²⁵⁴ The primary endpoint was CR (no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. A total of 1,369 patients were randomized to rolapitant regimen or control therapy. Patients ranged from 22 to 88 years of age, with a mean age of 57 years. A significantly greater proportion of patients receiving rolapitant had completed responses in the delayed phase of nausea and vomiting than patients in the control group (71% versus 62%; p=0.0002).

Postoperative Nausea and Vomiting (PONV)

aprepitant (Emend) versus ondansetron (Zofran)

Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study.²⁵⁵ Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo)

within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($p=0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% versus 21%, $p=0.0419$) and 24 hours (14% versus 36%, $p=0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% versus 60%), nausea scores, need for rescue antiemetics (65% versus 60%), CR (no post-operative nausea and vomiting [PONV] and no rescue, 22% versus 36%), or patient satisfaction with the management of PONV.

Aprepitant/dexamethasone was more effective than ondansetron/dexamethasone for prophylaxis against post-operative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in CR between the groups.

aprepitant (Emend) plus ondansetron (Zofran) versus placebo plus ondansetron (Zofran)

A prospective, randomized, double-blind study was performed to assess the occurrence of PONV and severity of nausea for up to 48 hours in 150 adult patients undergoing plastic surgery.²⁵⁶ Patients were randomized to take 40 mg of oral aprepitant plus 4 mg IV ondansetron (Group A, $n=75$) or oral placebo plus 4 mg IV ondansetron (Group B, $n=75$). Oral aprepitant or placebo was given to patients 2 hours prior to their scheduled operation. All patients in both groups received the same anesthetic regimen and 4 mg of IV ondansetron during surgery. All patients from both groups were allowed any of the institution's formulary anti-emetics and/or pain medications post-operatively. A blinded investigator recorded the occurrence of nausea and vomiting before surgery, on admission to the post-anesthesia unit, and hourly until the patient was discharged using a verbal rating scale. Retching and vomiting were evaluated as a 'yes' or 'no'. After discharge, patients rated their nausea, vomiting, and retching using the same scale and logged which analgesics they used. No patients experienced vomiting before being admitted to the post-anesthesia care unit. All episodes of vomiting occurred in the first 12 hours after being admitted to the post-anesthesia care unit. Patients in Group A (9.3%) experienced less vomiting than those in Group B (29.7%, $p=0.003$), indicating a relative risk reduction of 31.3%. Using a Kaplan-Meier plot the hazards of vomiting 12 hours post-surgery indicated an increase incidence of vomiting in Group B ($p=0.006$). No patient in Group A or B experienced vomiting 12 hours after being admitted to the post-anesthesia care unit. The reported mean nausea scores for Group A were lower than Group B, 5 and 8, respectively ($p=0.014$). The severity of nausea was higher in Group B ($p=0.24$). There were no significant differences in anti-emetic usage (42.7% in Group A and 44.6% in Group B) or CR (absence of vomiting and no need of rescue anti-emetic medications) between Group A and Group B (26 patients and 20 patients, respectively, $p=0.288$). The study concluded aprepitant decreases post-operative nausea and vomiting and is useful when used in combination with other antiemetics for post-operative nausea and vomiting.

dolasetron (Anzemet) versus ondansetron (Zofran) in pediatric patients

In a randomized, placebo-controlled, double-blind trial, oral dolasetron and ondansetron were compared in preventing post-operative N/V in 150 children after various surgical operations.²⁵⁷ Children were assigned randomly to 1 of 3 groups to receive dolasetron 1.8 mg/kg, ondansetron 0.15 mg/kg, or a placebo. All children received methylene blue capsules orally as an indicator before the induction of anesthesia. Post-operative contamination of the mouth and the endotracheal tube by methylene blue, and post-operative N/V were recorded for 24 hours. In the 1-hour period after the

operation, there were no differences between the groups. During the period 1 to 24 hours after surgery, dolasetron was significantly better than placebo (incidence: 16% with dolasetron versus 48% with placebo for overall nausea and vomiting). Over the entire 24 hours, both dolasetron and ondansetron were significantly better than placebo (incidence: 32% with dolasetron and 48% with ondansetron versus 78% with placebo for overall nausea and vomiting). There were no significant differences between dolasetron and ondansetron, and no important adverse events were reported.

granisetron versus ondansetron (Zofran)

A randomized, cross-over pilot study of PONV was conducted in 250 female patients who received prophylactic ondansetron 4 mg at the end of a surgical procedure requiring general anesthesia.²⁵⁸ Women were then followed post-operatively for 4 hours. Eighty-eight of the women developed PONV and were randomly assigned to receive 1 of the following: a repeat dose of ondansetron 4 mg (n=30), granisetron 1 mg (n=30), or granisetron 0.1 mg (n=28). They were followed for 24 hours. Patients who received the repeat dose of ondansetron had a CR of 57%, those receiving granisetron 1 mg or 0.1 mg had CRs of 60% and 68%, respectively. This difference was not statistically significant (p=0.773).

The efficacy of oral granisetron and oral ondansetron was compared for preemptive antiemesis in women undergoing modified radical mastectomy.²⁵⁹ A randomized, double-blind, controlled study assigned 90 women, aged 18 to 65 years old, scheduled to receive radical mastectomies to receive oral granisetron 2 mg, ondansetron 4 mg, or placebo (30 women in each group) 1 hour before induction of anesthesia. PONV was assessed until 24 hours post surgery. A CR in 0 to 2 hours after anesthesia was found in 43%, 63%, and 90% of patients who had received placebo, granisetron, or ondansetron, respectively; of these, the percentages of patients requiring rescue antiemetics were 40%, 17%, and 7%. The presence of N/V was less than 23% after 2 hours in all 3 groups. In addition, after 2 hours, N/V scores and need for antiemetics were similar in all 3 groups. Oral ondansetron 4 mg provided better preemptive antiemesis than oral granisetron 2 mg and placebo in the 2 hours following surgery with general anesthesia.

ondansetron (Zofran) versus palonosetron (Aloxi)

A prospective randomized, double-blind trial comparing ondansetron and palonosetron was conducted in 100 adult female patients undergoing total thyroidectomy to assess nausea and vomiting, severity of nausea, use of post-operative nausea and pain rescue medication, severity of pain, and side effects at 0 to 2 hours and 2 to 24 hours post-operation.²⁶⁰ With the exception of the study drugs all medications used during the surgery and in the patient-controlled analgesia (PCA) pump after surgery were the same between the 2 groups. After the surgery, patients were randomized to receive a bolus of 8 mg ondansetron (n=50) and 16 mg added to the PCA or a bolus of 0.075 mg palonosetron (n=50) and 8 mL of normal saline added to the PCA. Patients were allowed rescue metoclopramide and meperidine, as needed, for nausea and vomiting and pain, respectively. At 0 to 2 hours post-operation there were no significant differences in the incidence of nausea and vomiting between the ondansetron and palonosetron groups. However, from 2 to 24 hours post-operation the incidence of nausea and vomiting was lower in the palonosetron group compared to the ondansetron group (p=0.03). The use of rescue anti-emetics was also lower in the palonosetron group versus the ondansetron group, 10% versus 28%, respectively, during the 2 to 24 hour study period (p=0.02). Overall, during the 24 hour post-operative period the incidence of nausea and vomiting was lower in the palonosetron versus ondansetron group (42% versus 62%; p=0.045). There was not a significant difference in pain or side effects between the palonosetron and ondansetron groups. The study concluded that a bolus injection

of palonosetron was more effective than combination bolus and IV ondansetron 2 to 24 hours post-operation for patients at high risk for post-operative nausea and vomiting.

ondansetron (Zofran) versus transdermal scopolamine (Transderm-Scop)

A randomized, double blind, multicenter trial of 620 at-risk female patients undergoing outpatient laparoscopic or breast augmentation surgery was conducted to compare the impact of combination therapy versus monotherapy in the reduction of PONV.²⁶¹ Patients received either an active transdermal scopolamine patch or a placebo patch 2 hours before entering the operating room. Patients also received ondansetron 4 mg shortly before induction of anesthesia. Response to antiemetics, time to rescue antiemetics, number of doses of rescue antiemetics, and severity and number of nausea and vomiting episodes were recorded. The combination of transdermal scopolamine and ondansetron statistically significantly reduced nausea and vomiting compared with ondansetron alone 24 hours after surgery. However, the same observations were not applicable at 48 hours post surgery. The proportion of patients who did not experience vomiting and did not use rescue medication was 48% for the combination group and 39% for the ondansetron group ($p < 0.02$). Total response (no nausea, no vomiting/retching, and no use of rescue medication) was also statistically higher for the combination group compared with the ondansetron-only group (35% versus 25%; $p < 0.01$). The time to first nausea, vomiting/retching, or rescue episode was statistically significantly longer for the combination group compared with the ondansetron-only group ($p < 0.05$).

Pregnancy Related Nausea and Vomiting

doxylamine/pyridoxine (Diclegis) versus placebo

A randomized, double-blind, placebo-controlled study was conducted to support the safety and efficacy of doxylamine/pyridoxine in the treatment of nausea and vomiting of pregnancy.^{262,263} Women ($n=256$) 18 years of age or older and 7 to 14 weeks gestation with nausea and vomiting of pregnancy were randomized to 14 days of doxylamine/pyridoxine or placebo. Two tablets of doxylamine/pyridoxine were administered at bedtime on day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of day 2, the patient could begin taking 1 tablet in the morning on day 3 in addition to 2 tablets at bedtime. If symptoms persisted on day 4, the patient could take an additional tablet in the afternoon. A maximum of 4 tablets (1 in the morning, 1 in the afternoon and 2 at bedtime) were taken daily. Over the treatment period, 19% of doxylamine/pyridoxine treated patients remained on 2 tablets daily, 21% received 3 tablets daily, and 60% received 4 tablets daily. The primary efficacy endpoint was the change from baseline at day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe). At baseline, the mean PUQE score was 9 in the doxylamine/pyridoxine arm and 8.8 in the placebo arm. There was a 0.7 (95% CI, 0.2 to 1.2; $p=0.006$) mean decrease from baseline in PUQE score at day 15 with doxylamine/pyridoxine compared to placebo. The only adverse effect that occurred in more than 5% of patients and exceeded the placebo rate was somnolence which occurred in 14.9% of patients in the doxylamine/pyridoxine group compared to 11.7% in the placebo group.

Generalized Nausea and Vomiting

ondansetron (Zofran) versus metoclopramide (Reglan) versus promethazine (Phenergan)

A randomized, placebo-controlled, double-blind superiority trial comparing ondansetron, metoclopramide, promethazine, and saline was conducted in 180 adult emergency room patients to assess the nausea reduction of ondansetron.²⁶⁴ Nausea was evaluated on a 100-mm VAS at baseline and then 30 minutes after treatment. Patients who have a VAS score of 40-mm or more were randomized to receive IV ondansetron 4 mg, metoclopramide 10mg, promethazine 12.5 mg, or saline in approximately 500 mL of saline hydration. A VAS reduction of 12-mm was considered clinically significant. There were 163 patients that completed the study with a median age of 32 years old and 68% were female. The median VAS reductions for ondansetron, metoclopramide, promethazine, and saline were -22, -30, -29, and -16, respectively, using the Kruskal-Wallis test (p=0.16). The study concluded that no evidence existed proving ondansetron was superior to metoclopramide and promethazine in the reduction of nausea in adult emergency room patients however early termination may have limited the detection of ondansetron's superiority over saline.

META-ANALYSES

Chemotherapy-Induced Nausea and Vomiting (CINV)

A meta-analysis compared the efficacy and safety of palonosetron with other 5-HT₃ receptor antagonists (dolasetron, ondansetron, granisetron) for prevention of CINV.²⁶⁵ The cumulative incidences of emesis were significantly lower in the patients treated with palonosetron on the first day (relative risk [RR], 1.11; 95% CI, 1.05 to 1.17), from 2 to 5 days (RR, 1.26; 95% CI, 1.16 to 1.36) and the overall 5 days (RR, 1.23; 95% CI, 1.13 to 1.34). No differences were found in safety. Another meta-analysis found similar results (5 studies; n=2,057) comparing palonosetron to ondansetron, granisetron, and dolasetron.²⁶⁶ They found that palonosetron resulted in less nausea, both acute (RR, 0.86; 95% CI, 0.76 to 0.96; p=0.007) and delayed (RR, 0.82; 95% CI, 0.75 to 0.89; p<0.00001). Patients using palonosetron also had less acute vomiting (RR, 0.76; 95% CI, 0.66 to 0.88; p=0.0002) and delayed vomiting (RR, 0.76; 95% CI, 0.68 to 0.85; p<0.00001) compared to the other 5-HT₃ receptor antagonists. An earlier meta-analysis did not find a difference between granisetron, ondansetron, and dolasetron.²⁶⁷ A similar systematic review and meta-analysis compared the role of 5-HT₃ receptor antagonists in CINV (26 studies).²⁶⁸ This meta-analysis also included a 5-HT₃ receptor antagonist that is not available in the U.S., tropisetron. The authors found that ondansetron had similar efficacy to granisetron and greater efficacy than dolasetron for acute vomiting. However, palonosetron demonstrated greater efficacy than ondansetron for both delayed nausea and acute and delayed vomiting.

A Cochrane review of the use of 5-HT₃ receptor antagonists in pediatrics found that additional research was needed to make any conclusions, but did find that the addition of dexamethasone to one of these agents may be beneficial in HEC (pending a risk/benefit assessment).²⁶⁹

A network meta-analysis of 36 trials (n=18,889) assessed the efficacy of NK₁ antagonist-inclusive triple regimens (NK₁ antagonist + 5HT₃ antagonist + dexamethasone) compared to duplex regimens (5HT₃ antagonist + dexamethasone) for the treatment CINV.²⁷⁰ Complete response (response in acute, delayed, and overall phases) was statistically superior with triple regimens in patients with HEC compared to duplex regimens (odds ratio [OR] across all phases, 0.47 to 0.66). In contrast, in patients

undergoing MEC, only aprepitant-based triple regimens had a statistically significant difference in complete response (OR, 0.52; 95% CI, 0.34 to 0.68). In addition, no statistically significant differences in efficacy (as measured by complete response) were noted between palonosetron-based triple regimens compared to first-generation 5HT₃ antagonist based regimens. No differences in treatment-emergent adverse effects between triple regimens.

Postoperative Nausea and Vomiting (PONV)

Multiple meta-analyses have compared the efficacy of 5-HT₃ receptor antagonists in PONV. One meta-analysis compared the efficacy of ondansetron and granisetron in early and total PONV. The risk ratio (RR) of ondansetron compared to granisetron in early PONV was 1.25, but it was not statistically significant (95% CI, 0.82 to 0.92; p=0.31). Likewise, the RR of ondansetron compared to granisetron in overall PONV was 1.13, but it was also not significant (95% CI, 0.82 to 1.56; p=0.46). Thus, the authors concluded that both agents were equally effective.²⁷¹

A meta-analysis assessed the compared the efficacy of palonosetron and ondansetron in PONV (9 RCTs; n=741).²⁷² They found that palonosetron was superior to ondansetron in both early (0 to 6 hours following surgery) and late (6 to 24 hours following surgery) postoperative nausea (relative risk [RR], 0.51 [95% CI, 0.37 to 0.71] and RR, 0.53 [95% CI, 0.36 to 0.77], respectively). A difference was also seen in late postoperative vomiting (RR, 0.41; 95% CI 0.28 to 0.62) but not in early postoperative vomiting (RR, 0.77; 95% CI, 0.45 to 1.34). A newer meta-analysis comparing palonosetron and ondansetron for PONV following a laparoscopic procedure (9 studies; n=834) found that there was no statistically significant difference between the 2 products in the first 24 hours following surgery (RR, 0.62; 95% CI, 0.35 to 1.1; I²=76%) and no differences in adverse effects (RR, 0.67; 95% CI, 0.4 to 1.14).²⁷³ However, palonosetron was more effective for the prevention of vomiting at 0 to 2 hours postoperatively (RR, 0.45; 95% CI, 0.26 to 0.78).

A network meta-analysis compared the efficacy of three 5-HT₃ receptor antagonists (ondansetron, granisetron, and dolasetron) during the first 24 hours for PONV prophylaxis (85 studies; n=15,269).²⁷⁴ The authors found that granisetron was superior to ondansetron (OR, 1.53; 95% CI, 1.15 to 2) and dolasetron (OR, 1.67; 95% CI, 1.12 to 2.38). Efficacy was similar among agents for vomiting and all agents were found to be superior to placebo.

A pairwise and network meta-analysis of 450 studies (n=80,410) assessed the efficacy of 5-HT₃ receptor antagonists for PONV.²⁷⁵ Overall, the following treatments were all considered effective compared to placebo for reduction of vomiting, with the exception of palonosetron and dexamethasone (OR, 1.43 [95% CI, 0.2 to 10.14]): ondansetron plus droperidol IV, granisetron plus dexamethasone, ondansetron plus metoclopramide IV, ondansetron plus dexamethasone, dolasetron plus dexamethasone, dolasetron plus droperidol IV, granisetron, granisetron plus droperidol IV, ondansetron, palonosetron, and dolasetron (238 trials; n=12,781; all OR < 1 and 95% CI < 1). Overall, the following treatments were all considered effective compared to placebo for the reduction of nausea, with the exceptions of palonosetron and dexamethasone (OR, 0.37 [95% CI, 0.12 to 1.1]) and metoclopramide IV plus ondansetron (OR, 0.3 [95% CI, 0.07 to 1.37]): dolasetron plus droperidol IV, granisetron plus dexamethasone, granisetron plus droperidol IV, dolasetron plus dexamethasone, ondansetron plus droperidol IV, ondansetron plus dexamethasone, palonosetron, granisetron, ondansetron, and dolasetron (195 trials; n=24,230; all OR < 1 and 95% CI < 1). All agents were more effective than placebo for PONV (125 trials; n=16,667; all OR < 1 and 95% CI < 1).

The same type of pairwise and network meta-analysis of 31 studies (n=6,623) found that significantly more patients receiving granisetron plus dexamethasone experienced an arrhythmia compared to placebo (OR, 2.96; 95% CI, 1.11 to 7.94) than other 5-HT₃ receptor antagonists (dolasetron: OR, 0.68 [95% CI, 0.44 to 1.04] and ondansetron plus dexamethasone: OR, 0.52 [95% CI, 0.16 to 1.68]).²⁷⁶

Ondansetron has demonstrated superiority over metoclopramide in another meta-analysis comparing the efficacy in PONV within 24 hours following laparoscopic cholecystectomy (OR, 0.33; 95% CI, 0.22 to 0.49; p<0.00001.²⁷⁷ A Cochrane review found that droperidol, metoclopramide, dolasetron, dexamethasone, and granisetron were all superior to placebo (RR varied from 0.6 to 0.8), but also noted that the results may have been affected by publication bias (737 studies; n=103,237).²⁷⁸

SUMMARY

The 5-HT₃ antagonists offer significant advantages in the prevention of nausea and vomiting (N/V) due to chemotherapy and radiotherapy. Based on available data, there appears to be little significant difference among the drugs in this class. The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) do not recommend one 5-HT₃ antagonist over another in moderately and highly emetogenic chemotherapy. Granisetron transdermal (Sancuso) may offer benefit to select patients undergoing moderate to highly emetogenic chemotherapy regimens who cannot tolerate other formulations. The transdermal formulation did demonstrate non-inferiority in efficacy to the oral formulation of granisetron. Granisetron extended-release injection (Sustol) offers a subcutaneous, long-acting treatment for the prevention of chemotherapy induced N/V and has demonstrated noninferiority with palonosetron (Aloxi). The ondansetron oral soluble film (Zuplenz) has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron (Zofran ODT).

Oral aprepitant (Emend), which must be taken for 3 days, can be used in combination with either dexamethasone or a 5-HT₃ receptor antagonist when treating chemotherapy-induced N/V or for use as monotherapy in prevention of post-operative N/V. The fosaprepitant for injection (Emend) and aprepitant injectable emulsion (Cinvanti) are dosed on day 1 only as adjunct to both moderate and highly emetogenic chemotherapy. The newest NK₁ receptor antagonist, oral and injectable emulsion rolapitant (Varubi), is also dosed once on day 1 of chemotherapy for either highly or moderately emetogenic chemotherapy regimens. **Intravenous fosnetupitant/palonosetron (Akynzeo)** and oral netupitant/palonosetron (Akynzeo) offer a single dosage combination of a substance P/NK₁ receptor antagonist and a 5-HT₃ receptor antagonist administered on the day of chemotherapy. The synthetic cannabinoids are recommended as second-line therapy for chemotherapy induced N/V when patients fail to respond adequately to conventional antiemetics. The significant risk for abuse and misuse, increased potential for drug interactions, and increased risk for psychotomimetic reactions that has not been observed with other oral antiemetics suggest the cannabinoids should be monitored closely and reserved for specific use only.

Doxylamine/pyridoxine (Diclegis, Bonjesta) is the only medication approved for the treatment of N/V of pregnancy in women who do not respond to conservative management. Diclegis is Pregnancy Category A, and there have not been any reports of congenital malformations with Bonjesta. Both doxylamine/pyridoxine formulations are associated with significant sedation.

REFERENCES

- 1 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 2 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.
- 3 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 4 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.
- 5 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.
- 6 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.
- 7 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.
- 8 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.
- 9 Sustol [package insert]. Redwood City, CA; Heron; May 2017.
- 10 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.
- 11 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.
- 12 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.
- 13 Zuplenz [package insert]. Portland, OR; Galena; July 2016.
- 14 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018.
- 15 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
- 16 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
- 17 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.
- 18 Syndros [package insert]. Chandler, AZ; Insys; September 2018.
- 19 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
- 20 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.
- 21 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
- 22 Reglan [package insert]. Baudette, MN; Ani; August 2017.
- 23 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 24 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 25 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
- 26 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
- 27 Tigan [package insert]. New York, NY; Pfizer; March 2017.
- 28 Naeim A, Dy SM, Lorenz KA, et al. Evidence-based recommendations for cancer nausea and vomiting. *J Clin Oncol*. 2008; 26: 3903-3910. Available at: <http://jco.ascopubs.org.ezproxy2.library.arizona.edu/content/26/23/3903.full.pdf+html>. Accessed November 26, 2018.
- 29 Ettinger DS, Berger MJ, Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 3.2018. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed November 26, 2018.
- 30 Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017 July 31. DOI: 10.1200/JCO.2017.74.4789. Available at: <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues>. Accessed November 26, 2018.
- 31 Ettinger DS, Berger MJ, Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 3.2018. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed November 26, 2018.
- 32 Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017 July 31. DOI: 10.1200/JCO.2017.74.4789. Available at: <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues>. Accessed November 26, 2018.
- 33 Ettinger DS, Berger MJ, Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 3.2018. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed November 26, 2018.
- 34 Fetting JH, Grochow LB, Folstein MF, et al. The course of nausea and vomiting after high-dose cyclophosphamide. *Cancer Treat Rep*. 1982; 66:1487-1493.
- 35 Morrow GR. A patient report measure for the quantification of chemotherapy induced nausea and emesis: Psychometric properties of the Morrow Assessment of Nausea and Emesis (MANE). *Br J Cancer*. 1992; 19:S72-S74 (suppl).
- 36 Willan A, Warr D, Pater J, et al. Methodological issues and antiemetic studies. In Osoba D, ed. *Effect of Cancer on Quality of Life*. Boca Raton, FL: CRC Press; 1991; 229-249.
- 37 Clark R, Tyson L, Frisone M. A correlation of objective (OBJ) and subjective (SUBJ) parameters in assessing antiemetic regimens (AER). *Oncol Nurs Forum*. 1985; 12:96(suppl).
- 38 Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017 July 31. DOI: 10.1200/JCO.2017.74.4789. Available at: <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues>. Accessed November 26, 2018.
- 39 Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017 July 31. DOI: 10.1200/JCO.2017.74.4789. Available at: <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues>. Accessed November 26, 2018.
- 40 Ettinger DS, Berger MJ, Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 3.2018. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed November 26, 2018.
- 41 Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017 July 31. DOI: 10.1200/JCO.2017.74.4789. Available at: <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues>. Accessed November 26, 2018.
- 42 Ettinger DS, Berger MJ, Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 3.2018. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed November 26, 2018.

- 43 Apfelbaum JL, Silverstein JH, Cung FF, et al. Practice guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. *Anesthesiology*. 2013; 118(2): 291-307. DOI: 10.1097/ALN.0b13e31827773e9. Available at: <https://www.asahq.org/>. Accessed November 26, 2018.
- 44 Diclegis for nausea and vomiting of pregnancy. *The Med Ltr Drugs Ther*. Aug. 5, 2013; 1422: 61.
- 45 American College of Obstetricians and Gynecologists. Nausea and vomiting of pregnancy. ACOG Practice Bulletin No. 189. *Obstet Gynecol*. 2018; 131(1):e15-e30. DOI: 10.1097/AOG.0000000000002456.
- 46 American College of Obstetricians and Gynecologists. Nausea and vomiting of pregnancy. ACOG Practice Bulletin No. 189. *Obstet Gynecol*. 2018; 131(1):e15-e30. DOI: 10.1097/AOG.0000000000002456.
- 47 Association of Professors of Gynecology and Obstetrics. Nausea and vomiting of pregnancy. APGO continuing series on women's health education. April 2015. Available at: <http://www.nationalperinatal.org/Resources/APGO%20Educational%20Series%202011.pdf>. Accessed November 26, 2018.
- 48 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 49 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 50 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.
- 51 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.
- 52 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.
- 53 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.
- 54 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.
- 55 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.
- 56 Sustol [package insert]. Redwood City, CA; Heron; May 2017.
- 57 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.
- 58 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.
- 59 Zuplenz [package insert]. Portland, OR; Galena; July 2016.
- 60 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.
- 61 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018
- 62 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
- 63 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.
- 64 Syndros [package insert]. Chandler, AZ; Insys; September 2018.
- 65 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
- 66 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.
- 67 Reglan [package insert]. Baudette, MN; Ani; August 2017.
- 68 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 69 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 70 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
- 71 Tigan [package insert]. New York, NY; Pfizer; March 2017.
- 72 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
- 73 Armstrong DM, Pickel VM, Joh TH, et al. Immunocytochemical localization of catecholamine synthesizing enzymes and neuropeptides in area postrema and medial nucleus tractus solitarius of rat brain. *J Comp Neurol*. 1982; 196:505-517.
- 74 Meller D, Vincent M. The emerging role of cannabinoid neuromodulators in symptom management. *Support Care Cancer*. 2007; 15: 63-71.
- 75 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 76 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 77 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.
- 78 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.
- 79 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.
- 80 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.
- 81 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.
- 82 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.
- 83 Sustol [package insert]. Redwood City, CA; Heron; May 2017.
- 84 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.
- 85 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.
- 86 Zuplenz [package insert]. Portland, OR; Galena; July 2016.
- 87 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.
- 88 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018
- 89 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
- 90 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.
- 91 Syndros [package insert]. Chandler, AZ; Insys; September 2018.
- 92 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
- 93 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.
- 94 Reglan [package insert]. Baudette, MN; Ani; August 2017.
- 95 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 96 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 97 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
- 98 Tigan [package insert]. New York, NY; Pfizer; March 2017.
- 99 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
- 100 Wang X, Zhang ZY, Powers D, et al. Bioequivalence of intravenous and oral rolapitant: Results from a randomized, open-label pivotal study. *J Clin Pharmacol*. 2017;57(12):1600-1606. DOI: 10.1002/jcph.966.
- 101 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
- 102 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.

103 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.

104 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.

105 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.

106 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.

107 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.

108 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.

109 Sustol [package insert]. Redwood City, CA; Heron; May 2017.

110 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.

111 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.

112 Zuplenz [package insert]. Portland, OR; Galena; July 2016.

113 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.

114 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018

115 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.

116 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.

117 Syndros [package insert]. Chandler, AZ; Insys; September 2018.

118 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.

119 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.

120 Reglan [package insert]. Baudette, MN; Ani; August 2017.

121 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.

122 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.

123 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.

124 Tigan [package insert]. New York, NY; Pfizer; March 2017.

125 Available at: www.clinicalpharmacology.com. Accessed February 21, 2018.

126 Available at: <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm592592.htm>. Accessed November 26, 2018.

127 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.

128 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.

129 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.

130 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.

131 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.

132 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.

133 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.

134 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.

135 Sustol [package insert]. Redwood City, CA; Heron; May 2017.

136 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.

137 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.

138 Zuplenz [package insert]. Portland, OR; Galena; July 2016.

139 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.

140 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018

141 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.

142 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.

143 Syndros [package insert]. Chandler, AZ; Insys; September 2018.

144 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.

145 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.

146 Reglan [package insert]. Baudette, MN; Ani; August 2017.

147 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.

148 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.

149 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.

150 Tigan [package insert]. New York, NY; Pfizer; March 2017.

151 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.

152 McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther. 2003; 74:17-24.

153 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.

154 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.

155 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.

156 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.

157 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.

158 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.

159 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.

160 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.

161 Sustol [package insert]. Redwood City, CA; Heron; May 2017.

162 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.

163 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.

164 Zuplenz [package insert]. Portland, OR; Galena; July 2016.

165 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.

166 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018

167 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.

168 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.
169 Syndros [package insert]. Chandler, AZ; Insys; September 2018.
170 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
171 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.
172 Reglan [package insert]. Baudette, MN; Ani; August 2017.
173 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
174 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
175 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
176 Tigan [package insert]. New York, NY; Pfizer; March 2017.
177 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
178 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
179 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
180 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.
181 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.
182 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.
183 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.
184 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.
185 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.
186 Sustol [package insert]. Redwood City, CA; Heron; May 2017.
187 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.
188 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.
189 Zuplenz [package insert]. Portland, OR; Galena; July 2016.
190 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.
191 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018
192 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
193 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.
194 Syndros [package insert]. Chandler, AZ; Insys; September 2018.
195 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
196 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.
197 Reglan [package insert]. Baudette, MN; Ani; August 2017.
198 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
199 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
200 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
201 Tigan [package insert]. New York, NY; Pfizer; March 2017.
202 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
203 Fujii Y, Tanaka H, Ito M. Preoperative oral granisetron for the prevention of vomiting after strabismus surgery in children. *Ophthalmology*. 1999; 106(9):1713–1715.
204 Fujii Y, Saitoh Y, Tanaka H, et al. Preoperative oral antiemetics for reducing postoperative vomiting after tonsillectomy in children: granisetron versus perphenazine. *Anesth Analg*. 1999; 88(6):1298-1301.
205 Fujii Y, Toyooka H, Tanaka H. Oral granisetron prevents postoperative vomiting in children. *Br J Anaesth*. 1998; 81(3):390–392.
206 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
207 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.
208 Cinvanti [package insert]. San Diego, CA; Heron; November 2017.
209 Emend for injection [package insert]. Whitehouse Station, NJ; Merck; September 2018.
210 Varubi [package insert]. Waltham, MA; Tesaro; March 2018.
211 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2016.
212 Granisetron injection [package insert]. Rockford, IL; Mylan; August 2017.
213 Granisetron tablet [package insert]. Eatontown, NJ; West-Ward; August 2016.
214 Sustol [package insert]. Redwood City, CA; Heron; May 2017.
215 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2017.
216 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2017.
217 Zuplenz [package insert]. Portland, OR; Galena; July 2016.
218 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; March 2017.
219 Aloxi [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2018
220 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
221 Marinol [package insert]. North Chicago, IL; Abbvie; August 2017.
222 Syndros [package insert]. Chandler, AZ; Insys; September 2018.
223 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
224 Metoclopramide HCl orally disintegrating tablet [package insert]. Baltimore, MD; Lupin; August 2017.
225 Reglan [package insert]. Baudette, MN; Ani; August 2017.
226 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
227 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
228 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
229 Tigan [package insert]. New York, NY; Pfizer; March 2017.
230 Available at: www.clinicalpharmacology.com. Accessed November 26, 2018.
231 Emend [package insert]. Whitehouse Station, NJ; Merck; May 2017.

- 232 Tesaro press release. Available at: <http://ir.tesarobio.com/news-releases/news-release-details/tesaro-announces-us-fda-approval-varubir-iv-delayed-nausea-and>. Accessed November 26, 2018.
- 233 Wang X, Zhang ZY, Powers D, et al. Bioequivalence of intravenous and oral rolapitant: Results from a randomized, open-label pivotal study. *J Clin Pharmacol*. 2017;57(12):1600-1606. DOI: 10.1002/jcph.966.
- 234 Bonjesta [package insert]. Bryn Mawr, PA; Duchesnay; June 2018.
- 235 de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol*. 2003; 21(22):4105-4111.
- 236 Albany C, Brames M, Fausel C, et al. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: A Hoosier Oncology Group Study. *J Clin Oncol*. 2012; 30:3998-4003.
- 237 Roila F, Ruggeri B, Ballatori E, et al. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double blind study. *J Clin Oncol*. 2014 Jan 10;32(2):101-6.
- 238 Kang HJ, Loftus S, Taylor A, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015; 16(4): 385-394. DOI: 10.1016/S1470-2045(15)70061-6.
- 239 Fauser AA, Duclos B, Chemaissani A, et al. Therapeutic equivalence of single oral doses of dolasetron mesylate and multiple doses of ondansetron for the prevention of emesis after moderately emetogenic chemotherapy. European Dolasetron Comparative Study Group. *Eur J Cancer*. 1996; 32A:1523-1529.
- 240 Meiri E, Jhangiani H, Vredenburg J, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin*. 2007; 23(3): 533-543.
- 241 Weinstein C, Jordan K, Green SA, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: results of a randomized, double-blind phase 3 trial. *Ann Oncol*. 2016; 27(1): 172-178. DOI: 10.1093/annonc/mdv482.
- 242 Schwartzberg L, Roeland E, Andric Z, et al. Phase III safety study of intravenous NEPA: a novel fixed antiemetic combination of fosnetupitant and palonosetron in patients receiving highly emetogenic chemotherapy. *Ann Oncol*. 2018;29(7):1535-1540. DOI: 10.1093/annonc/mdy169.
- 243 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2017.
- 244 Fox-Geiman MP, Fisher SG, Kiley K, et al. Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. *Biol Blood Marrow Transplant*. 2001; 7:596-603.
- 245 Noble A, Bremer K, Goedhals L, et al. A double-blind, randomized, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. The Granisetron Study Group. *Eur J Cancer*. 1994; 30A(8):1083-1088.
- 246 Sustol [package insert]. Redwood City, CA; Heron; May 2017.
- 247 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
- 248 Akynzeo [package insert]. Iselin, NJ; Helsinn; April 2018.
- 249 Aapro-Piacentini M, Rugo H, Rossi G, et al. A randomized Phase 3 study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol*. 2014; 25(7):1328-33. DOI: 10.1093/annonc/mdu101.
- 250 Pectasides D, Dafni U, Aravantios G, et al. A randomized trial to compare the efficacy and safety of antiemetic treatment with ondansetron and ondansetron zydys in patients with breast cancer treated with high-dose epirubicin. *Anticancer Res*. 2007; 27(6C):4411-4117.
- 251 Roscoe J, Heckler C, Morrow G, et al. Prevention of delayed nausea: A University of Rochester cancer center community clinical oncology program study of patients receiving chemotherapy. *J Clin Oncol*. 2012; 30:3389-3395.
- 252 Schwartzberg L, Barbour SY, Morrow GR, et al. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). *Support Care Cancer*. 2014 Feb;22(2):469-77. DOI: 10.1007/s00520-013-1999-9.
- 253 Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. *Lancet Oncol*. 2015 Sep;16(9):1079-89. DOI: 10.1016/S1470-2045(15)00035-2.
- 254 Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. *Lancet Oncol*. 2015 Sep; 16(9): 1071-8. DOI: 10.1016/S1470-2045(15)00034-0.
- 255 Habib AS, Keifer JC, Borel CO, et al. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. *Anesth Analg*. 2011; 112(4):813-8.
- 256 Vallejo M, Phelps A, Ibinson, J, et al. Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery. *Plastic and Reconstructive Surgery*. 2012; 129(2): 519-526.
- 257 Karamanlioglu B, Turan A, Memis D, et al. Comparison of oral dolasetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in children. *Eur J Anaesthesiol*. 2003; 20(10):831-835.
- 258 Candiotti KA, Nhuch F, Kamat A, et al. Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study. *Anesth Analg*. 2007; 104(6):1370-1373.
- 259 Bhatnagar S, Gupta A, Mishra S, et al. Preemptive antiemesis in patients undergoing modified radical mastectomy: oral granisetron versus oral ondansetron in a double-blind, randomized, controlled study. *J Clin Anesth*. 2007; 19(7):512-516.
- 260 Moon Y, Joo J, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. *British Journal of Anaesthesia*. 2012; 108(3): 417-422.
- 261 Gan T, et al. A Randomized, Double-Blind, Multicenter Trial Comparing Transdermal Scopolamine Plus Ondansetron to Ondansetron Alone for the Prevention of Postoperative Nausea and Vomiting in the Outpatient Setting. *Anesth Analg*. 2009; 108:1498-504.
- 262 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay USA; June 2018.
- 263 Koren G, Clark S, Hankins GDV, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *Am J Obstet Gynecol*. 2010; 203(6):571.e1-7.

-
- 264 Barrett T, DiPersio D, Jenkins C, et al. A randomized, placebo-controlled trial of ondansetron, metoclopramide, and promethazine in adults. *Am J Emerg Med.* 2011; 29(3):247–255.
- 265 Jin Y, Sun W, Gu D, et al. Comparative efficacy and safety of palonosetron with the first 5-HT₃ receptor antagonists for the chemotherapy induced nausea and vomiting: a meta-analysis. *Eur J Cancer Care.* 2013; 22(1): 41-50. DOI: 10.1111/j.1365-2354.2012.01353.x.
- 266 Botrel TE, Clark OA, Clark L, et al. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT₃R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. *Support Care Cancer.* 2011; 19(6): 823-832. DOI: 10.1007/s00520-010-0908-8.
- 267 Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT₃-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer.* 2007; 15(9): 1023-1033.
- 268 Simino GP, Marra LP, Andrade EI, et al. Efficacy, safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT₃RA) used to control chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. *Expert Rev Clin Pharmacol.* 2016; 9(9): 1183-1194. DOI: 10.1080/17512433.2016.1190271.
- 269 Phillips RS, Gopaul S, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. *Cochrane Database Syst Rev.* 2010; 9: CD007786. DOI: 10.1002/14651858.CD007786.pub2.
- 270 Zhang Y, Yang Y, Zhang Z, et al. Neurokinin-1 receptor antagonist-based triple regimens in preventing chemotherapy-induced nausea and vomiting: a network meta-analysis. *J Natl Cancer Inst.* 2016; 109(2).
- 271 Wu SJ, Xiong XZ, Lin YX, et al. Comparison of the efficacy on ondansetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech.* 2013; 23(1): 79-87. DOI: 10.1097/SLE.0b013e31827549e8.
- 272 Xiong C, Liu G, Ma R, et al. Efficacy of palonosetron for preventing postoperative nausea and vomiting: a systematic review and meta-analysis. *Can J Anesth.* 2015; 62(12): 1268-1278. DOI: 0.1007/s12630-015-0457-1.
- 273 Liu Q, Zhou C, Bao Z, et al. Effects of palonosetron and ondansetron on preventing nausea and vomiting after laparoscopic surgery. *J Int Med Res.* 2018;46(1):411-420. DOI: 10.1177/0300060517715374.
- 274 Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for post-operative nausea and vomiting prophylaxis. *Clin Ther.* 2012; 34(2): 282-294. DOI: 10.1016/j.clinthera.2012.01.007.
- 275 Tricco AC, Soobiah, Blondal E, et al. Comparative safety of serotonin (5-HT₃) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med.* 2015; 13: 136. DOI: 10.1186/s12916-015-0371-y.
- 276 Tricco AC, Soobiah C, Blondal E, et al. Comparative safety of serotonin (5-HT₃) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med.* 2015; 13: 142. DOI: 10.1186/s12916-015-0379-3.
- 277 Wu SJ, Xiong Xz, Cheng TY, et al. Efficacy of ondansetron vs. metoclopramide in prophylaxis of postoperative nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. *Hepatogastroenterology.* 2012; 59 (119): 2064-2074.
- 278 Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev.* 2006; 3:CD004125.