



Antiemetics/Antivertigo Agents

Therapeutic Class Review (TCR)

February 15, 2013

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Road, Suite 201
Cincinnati, Ohio 45242

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReEditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Antiemetic Drugs	Manufacturer	Indication(s)
NK₁ receptor antagonist		
aprepitant (Emend®) ¹	Merck	In combination with other antiemetic agents for: <ul style="list-style-type: none"> Prevention of acute and delayed nausea and vomiting (N/V) associated with highly emetogenic cancer chemotherapy (initial and repeat dosing), including high-dose cisplatin Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Prevention of post-operative N/V
fosaprepitant dimeglumine (Emend® for injection) ²	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 Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
5-HT₃ antagonists		
dolasetron (Anzemet®) ^{3,4}	Sanofi-Aventis	Oral tablets: <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 two years of age and older Prevention of post-operative N/V in adults and children two years of age and older Injection: Prevention/treatment of post-operative N/V
granisetron (GranisoI™) ^{5,6}	generic, Pediatrix	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 transdermal (Sancuso®) ⁷	ProStrakan	Prevention of N/V in patients receiving moderately or highly emetogenic chemotherapy regimens of up to five consecutive days duration
ondansetron (Zofran®, Zuplenz®) ^{8,9,10}	generic, GlaxoSmithKline, Par Pharmaceuticals	Oral and Injectable: <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 Oral: <ul style="list-style-type: none"> Prevention of N/V associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq 50 \text{ mg/m}^2$ 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®) ¹¹	Eisai	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

FDA-Approved Indications (continued)

Antiemetic Drugs	Manufacturer	Indication(s)
Cannabinoids		
dronabinol (Marinol®) ¹²	generic, Abbott	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®) ¹³	Meda Pharmaceuticals	Treatment of N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
Antidopaminergic Agents		
metoclopramide (Reglan®) ^{14,15,16}	generic, Ani Pharmaceuticals	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
metoclopramide (Metozolv® ODT) ¹⁷	Salix Pharmaceuticals	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)
Others¹⁸		
phosphorated carbohydrate solution (Emetrol® OTC)	WellSpring	Relief of nausea due to upset stomach from intestinal flu, stomach flu, and food or drink indiscretions.
trimethobenzamide (Tigan®)	generic, JHP Pharmaceuticals	Treatment of N/V associated with gastroenteritis

Antivertigo Drugs ^{19,20}	Manufacturer	Indication(s)
Antihistamines		
cyclizine (Cyclivert® OTC, , Marezine® OTC)	L aser, Himmel	Treatment and prevention of N/V and dizziness associated with motion sickness
dimenhydrinate (Dramamine® OTC)	generic, McNeil	Treatment and prevention of motion sickness Treatment of N/V
diphenhydramine (Benadryl®)	generic, McNeil	Treatment and prevention of N/V associated with motion sickness
meclizine (Antivert®, Bonine®, Dramamine® Less Drowsy OTC)	generic, Pfizer, , Insight, McNeil	Treatment and prevention of N/V associated with motion sickness

FDA-Approved Indications (continued)

Antivertigo Drugs ^{21,22}	Manufacturer	Indication(s)
Phenothiazines		
promethazine (Phenergan®)	generic, West-Ward	Treatment and prevention of N/V associated with motion sickness Prevention and control of N/V associated with certain types of anesthesia and surgery
prochlorperazine (Compro®)	generic, Paddock Labs	For control of severe N/V For preoperative nausea control For treatment of N/V
Anticholinergics		
scopolamine (Transderm-Scop®)	generic, Novartis	Treatment and prevention of motion sickness Prevention of post-operative N/V For the treatment of N/V

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 percent of all cancer patients receiving chemotherapy experience nausea and/or vomiting, whereas 10 to 44 percent experience anticipatory nausea and/or vomiting. Furthermore, more than 90 percent of patients using highly emetogenic chemotherapeutic agents will experience acute emesis. However, only approximately 30 percent of these patients will vomit if they receive an antiemetic prior to their highly emetogenic chemotherapeutic treatment.²³

There are several different factors which 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.²⁴

The goal of antiemetic therapy is to prevent nausea and vomiting (N/V) completely. As a result of research over the last 20 years, this goal is achieved for many patients receiving chemotherapy or radiation therapy. Research has increased understanding of the pathophysiology of these symptoms and has resulted in therapy that is more effective and safer than in the past. With currently available agents, complete control of emesis (e.g., no vomiting) is achievable in the majority of patients in the first 24 hours and in approximately 45 percent of patients during the first week of chemotherapy.^{25,26} 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).^{27,28,29} The incidence of nausea correlates well with the incidence of vomiting, although chemotherapy-induced nausea occurs at a greater frequency.^{30,31} Total control (no nausea or vomiting) is ideal, but lesser control rates such as

major control (fewer than three emetic episodes) or minor control (three to five 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. The v1.2013 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.³² Furthermore, the v1.2013 NCCN Antiemesis guidelines state that antiemetic therapy should be initiated prior to 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.³³

Newer antiemetic regimens are more convenient for patients to receive and for healthcare professionals to administer. As antiemetic usage has grown, the classes of agents for treatment, the agents available, and their indications have increased in number, as well. The prevention and treatment of cancer chemotherapy- and radiotherapy-related N/V have come to be based largely on the use of type-3 serotonin (5-HT₃) receptor antagonists.³⁴ Aprepitant (Emend), a neurokinin-1 (NK₁) receptor antagonist, is used in combination with a corticosteroid and a 5-HT₃ receptor antagonist when treating chemotherapy-induced N/V. The cannabinoids are synthetic delta-9 tetrahydrocannabinol (THC) products and include two products, dronabinol (Marinol) and nabilone (Cesamet).

Prior to the most recent expert guidelines the ASCO, the Multinational Association of Supportive Care in Cancer (MASCC), the American Society of Health-System Pharmacists (ASHP), and the v1.2013 NCCN guidelines all concluded that serotonin receptor antagonists had equivalent safety and efficacy and could be used interchangeably at equivalent doses.^{35,36,37,38} However, the updated 2011 ASCO and v1.2013 NCCN guidelines now suggest that palonosetron (Aloxi) demonstrates superiority in preventing emesis due to high or moderate risk chemotherapy agents compared to other 5-HT₃ medications especially in delayed emesis.³⁹ Conversely, the 2011 MASCC guidelines concluded due to the shortcomings of the studies comparing palonosetron to other 5-HT₃ medications they could not recommend palonosetron as having a preferred 5-HT₃ status at this time and more studies are warranted.^{40,41,42} The v1.2013 NCCN Antiemesis guidelines confirm the various routes of administration for antiemetics including oral, rectal, intravenous (IV), intramuscular (IM), and transdermal. Oral antiemetics remain equally effective, safe, more convenient, and often less costly than other routes of administration. Although studies may show these agents to be equally effective on a population basis, individual patients may respond differently to them.

The 2011 ASCO and 2011 MASCC current guidelines have incorporated aprepitant (Emend) into first-line therapy for patients on chemotherapy of high emetic risk (with a 5-HT₃ antagonist and dexamethasone), patients receiving an anthracycline and cyclophosphamide (with a 5-HT₃ antagonist and dexamethasone), and the prevention of delayed emesis with agents of high emetic risk (with dexamethasone). For patients receiving other chemotherapy of moderate emetic risk or radiation therapy of high emetic risk, a two-drug regimen of a 5-HT₃ receptor serotonin antagonist and dexamethasone are recommended. In the 2011 MASCC guidelines, palonosetron plus dexamethasone is recommended for patients receiving moderately emetogenic chemotherapy (except an anthracycline plus cyclophosphamide).⁴³ According to the ASCO guidelines,⁴³ patients receiving moderately emetic radiation therapy should receive a 5-HT₃ antagonist.⁴⁴

The v1.2013 NCCN Antiemesis guidelines identify emesis prevention treatment options for high, moderate, low, and minimal emetic risk IV chemotherapy, oral chemotherapy, as well as breakthrough

treatment for chemotherapy-induced N/V. For patients receiving IV chemotherapy with high emetic risk, an oral, transdermal, or IV formulation of a 5-HT₃ antagonist, corticosteroid, and NK₁ receptor antagonist should be initiated prior to the chemotherapy. For patients receiving IV chemotherapy with moderate emetic risk, an oral or IV regimen of a 5-HT₃ antagonist and a corticosteroid with or without a NK₁ receptor antagonist should be initiated one day prior to the start of chemotherapy. On days two to three of this regimen, three options are possible: 5-HT₃ antagonist monotherapy, corticosteroid monotherapy, or a NK₁ receptor antagonist. For patients who receive low emetic risk IV chemotherapy, alternative options may include oral or IV formulations of dexamethasone, prochlorperazine (Compro), or metoclopramide (Reglan). There is no routine prophylaxis for patients who receive minimal emetic risk IV chemotherapy. For patients who receive oral chemotherapy where prophylaxis is recommended, an oral 5-HT₃ antagonist should be initiated prior to chemotherapy. Conversely, for patients who receive oral chemotherapy where no prophylaxis or as needed prophylaxis is recommended, patients may receive alternative agents like metoclopramide (Reglan) or prochlorperazine (Compro). If N/V persists, then an oral serotonin antagonist could be initiated. Finally, for breakthrough treatment of chemotherapy-induced N/V, the general principle is to add one agent from a different class as needed to the existing regimen (e.g., antipsychotic, benzodiazepine, cannabinoid, dopamine receptor antagonist, phenothiazine, serotonin antagonist, or corticosteroid). Based on response to the breakthrough treatment, the antiemetic therapy is adjusted and/or modified.

Motion sickness is the result of a conflict between the various senses in regard to motion. The semicircular canals and otoliths in the inner ear sense angular and vertical motion, while the eyes and the proprioceptors determine the body's position in space. When signals received by the eyes or the proprioceptors do not match those being transmitted by the inner ear, motion sickness occurs. It can occur in either the presence or absence of actual motion, such as when viewing a slide through a microscope. Symptoms include nausea, vomiting, pallor, sweating, and often a sense of impending doom. There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications typically cause drowsiness or similar adverse effects.⁴⁵

PHARMACOLOGY

NK₁ receptor antagonist [aprepitant (Emend)⁴⁶, fosaprepitant (Emend for Injection)]⁴⁷

Aprepitant (Emend) 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.⁴⁸ Aprepitant (Emend) has little or no affinity for 5-HT₃, dopamine, or corticosteroid receptors. Fosaprepitant (Emend for injection) is a prodrug of aprepitant (Emend) and is quickly converted to aprepitant (Emend) when administered intravenously.

5-HT₃ antagonists [dolasetron (Anzemet), granisetron (Granisol), granisetron transdermal (Sancuso), ondansetron (Zofran, Zuplenz), palonosetron (Aloxi)]^{49,50,51,52,53,54,55}

Dolasetron (Anzemet), granisetron (Granisol, Sancuso), ondansetron (Zofran, Zuplenz), and palonosetron 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 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.

Cannabinoids [dronabinol (Marinol), nabilone (Cesamet)]^{56,57,58}

Dronabinol (Marinol) and nabilone (Cesamet) act on the cannabinoid receptors (CB1 and CB2) in the brain. 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)]^{59,60,61}

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.

Phenothiazines [promethazine (Phenergan), prochlorperazine (Compro)]^{62,63}

The phenothiazines block postsynaptic dopaminergic receptors in the brain including the chemoreceptor trigger zone (CTZ). This mechanism contributes to depression of the reticular activating system and affects basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. Promethazine also has both antihistaminic and anticholinergic properties.

Antihistamines [cyclizine (Cyclivert OTC), dimenhydrinate (Dramamine OTC), diphenhydramine (Benadryl), meclizine (Antivert, Univert)]^{64,65}

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.

Anticholinergics [scopolamine (Transderm-Scop)]^{66,67}

It is suggested that scopolamine (Transderm-Scop) exerts its activity in the central nervous system by blocking activity to the vomiting center and vestibular nuclei.

PHARMACOKINETICS

Antiemetics				
Drug	Bioavailability (%)	Half life (t1/2) (hr)	Metabolites	Excretion (%)
NK₁ receptor antagonist				
aprepitant (Emend) ⁶⁸	60-65	9-13	7, weakly active	urine: 57 feces: 45
fosaprepitant (Emend for Inj) ⁶⁹	--	9-13	prodrug converted to aprepitant	urine: 57 feces: 45
5-HT₃ antagonists				
dolasetron (Anzemet) ^{70, 71}	75 (oral)	8.1(oral) 7.3(IV)	hydrodolasetron, active	oral -urine: 61 feces: 39 IV - urine: 53
granisetron (Granisol) ^{72,73}	--	6.2 (oral) 4.91-8.95 (IV)	yes, activity questionable	oral -urine: 48 feces: 38 IV - urine: 49 feces: 34
granisetron transdermal (Sancuso) ⁷⁴	--	N/A; drug is released from patch continuously	yes	urine: 49 feces: 34
ondansetron (Zofran, Zuplenz) ^{75,76,77}	56 (oral)	3.1-6.2 (oral) 2.5-6.7 (IV)	yes, none significant	urine: 5
palonosetron (Aloxi) ⁷⁸	--	≈40	yes	feces: 5 to 8 urine: 80
Cannabinoids				
dronabinol (Marinol) ⁷⁹	10-20	25-36	yes, one active	urine: 10-15 feces: 50
nabilone (Cesamet) ^{80,81}	5-20	2-35	yes, active and inactive	urine: 24 feces: 60
Antidopaminergics^{82,83}				
metoclopramide (Reglan)	65-95	5-6	None	urine: 85 feces:2
metoclopramide (Metozolv ODT) ⁸⁴				
Others^{85,86}				
phosphorated carbohydrate solution (Emetrol OTC)	--	--	--	--
trimethobenzamide (Tigan)	60-100	7-9	yes, one active	urine:30-50

Granisetron transdermal patch (Sancuso) delivers 66 percent of active ingredient following application for seven days.

Pharmacokinetics (continued)

Antivertigo Agents^{87,88}				
Drug	Bioavailability (%)	Half life (t1/2) (hr)	Metabolites	Excretion (%)
Antihistamines				
cyclizine (Cyclivert OTC)	--	13	yes, one active	urine: <1
dimenhydrinate (Dramamine OTC)	--	3.5	yes, one active	--
diphenhydramine (Benadryl)	65-100	2.4-9.3	yes, five active	urine: 50-75
meclizine (Antivert, Bonine, Univert)	--	6	yes, one active	--
Phenothiazines				
promethazine (Phenergan)	low	10-14	yes, one active	--
prochlorperazine (Compro)	12.5	6-10 (single dose) 14-22 (repeat dosing)	yes; one active	--
Anticholinergics				
scopolamine (Transderm-Scop)	--	--	yes	urine: 34

CONTRAINDICATIONS/WARNINGS^{89,90,91,92,93,94,95,96,97,98,99,100}

Aprepitant and fosaprepitant (Emend) are contraindicated in patients who are hypersensitive to any component of the product. Known hypersensitivity reactions include flushing, erythema, dyspnea, and anaphylactic reactions. Aprepitant and fosaprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. 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 percent of patients receiving aprepitant in clinical trials.

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. These reactions have not been seen with dolasetron (Anzemet).

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. ECG changes have occurred in patients using ondansetron (Zofran, Zuplenz) and dolasetron (Anzemet), including QT interval prolongation and Torsade 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.

Granisetron (Granisol) and ondansetron (Zofran, Zuplenz) do not stimulate gastric or intestinal peristalsis. They should not be used instead of nasogastric suction. Their use in patients following abdominal surgery or in chemotherapy-induced N/V may mask a progressive ileus and/or gastric distention. Granisetron injection contains benzyl alcohol and has been associated with serious adverse reactions and death especially in neonates.

Dolasetron solution administered intravenously is contraindicated in adult and pediatric patients for the prevention of N/V associated with initial and repeat courses of emetogenic cancer chemotherapy due to dose dependent 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 (Anzemet) 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.

Patients with phenylketonuria should be informed that ondansetron orally disintegrating tablets (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) is contraindicated in patients with any known sensitivities to dronabinol, cannabinoid oil, sesame oil, or any other of its ingredients. Nabilone (Cesamet) is contraindicated in patients with a hypersensitivity to any cannabinoid.

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 including dizziness, drowsiness, euphoria, disorientation, depression, hallucinations, anxiety, and psychosis.

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 (Marinol) 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 preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

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.

Metoclopramide has a black box warning for chronic long-term or high-dose use that 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.

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.¹⁰¹

Promethazine (Phenergan) and prochlorperazine (Compro) are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to phenothiazines. Promethazine tablets and prochlorperazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function. Prochlorperazine should be used cautiously in patient populations with pheochromocytoma as prochlorperazine-induced buildup of neurotransmitters can result in a cardiotoxic effect.

Transderm-Scop is contraindicated in persons who are hypersensitive to the drug scopolamine or to other belladonna alkaloids, or to any ingredient or component in the formulation or delivery system, or in patients with angle-closure (narrow angle) glaucoma.

REMS (Risk Evaluation and Mitigation Strategy)

Metoclopramide (Reglan, Metozolv ODT) has a REMS advising of the risk of tardive dyskinesia with chronic use. Treatment for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing this condition.

DRUG INTERACTIONS

aprepitant (Emend)¹⁰² and fosaprepitant dimeglumine (Emend for Injection)¹⁰³

Aprepitant and fosaprepitant (Emend) 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 intravenous (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 125mg/80mg 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, troleandomycin, 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 percent) decrease in INR. In patients on warfarin, INR should be closely monitored at seven to 10 days following initiation of the three-day regimen of aprepitant with each chemotherapy cycle or after a single aprepitant 40 mg dose for the prevention of postoperative nausea and vomiting.

Coadministration with fosaprepitant or aprepitant, may reduce the efficacy of hormonal contraceptives such as oral contraceptives, transdermal patches, implants, and certain 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 one 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 percent when coadministered with aprepitant .¹⁰⁴

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.

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

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

5-HT₃ receptor antagonists^{105,106,107,108,109,110,111,112}

Dolasetron (Anzemet), granisetron (Granisol, Sancuso), palonosetron (Aloxi), and ondansetron (Zofran, Zuplenz) are metabolized by various CYP450 enzymes; however, due to the variety of enzymes involved, no clinically significant drug interactions have been identified at this time.

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. Due to granisetron (Granisol) being metabolized by the cytochrome P-450 system, taking this medication with enzyme inducers or inhibitors could affect the clearance of granisetron (Granisol).

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

Blood levels of hydrodolasetron increased 24 percent when dolasetron was coadministered with cimetidine (nonselective inhibitor of CYP450) for seven days and decreased 28 percent with coadministration of rifampin (potent inducer of CYP450) for seven days. Blood levels of hydrodolasetron decreased approximately 27 percent when intravenous dolasetron was administered with atenolol.

Caution should be exercised when dolasetron is coadministered with drugs, including those used in chemotherapy and surgery that prolong ECG intervals and/or cause hypokalemia or hypomagnesemia.

QT prolongation has been reported with granisetron (Granisol). The use of granisetron (Granisol) in patients concurrently treated with drugs known to prolong the QT interval and/or is arrhythmogenic may result in clinical consequences.

Cannabinoids^{113,114}

Both of the cannabinoids, dronabinol (Marinol) 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.

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

Antidopaminergics^{115,116,117}

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, and 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.

Phenothiazines^{118,119}

Prochlorperazine (Compro) may diminish the effect of dopamine agonists (antiparkinson's agents). Prochlorperazine may enhance the toxic effects of antipsychotics and enhance CNS depressant effects of opioids, barbiturates and other CNS agents. Promethazine (Phenergan) is a major substrate of CYP2D6; therefore, monitor therapy with CYP2D6 inhibitors or inducers. Avoid combination with metoclopramide (Reglan, Metozolv ODT) or serotonin modulators.

Phenothiazines have been reported to prolong the QT interval. Taking phenothiazines with other medications known to prolong QT intervals should be avoided.

Caution should be used when phenothiazines are used with other drugs with antimuscarinic activity as side effects may be potentiated.

Caution should be used when phenothiazines are used with CNS depressants such as anxiolytics, sedatives, and hypnotics as additive depressive CNS effects could occur.

Phenothiazines can lower the seizure threshold and dose adjustments of anticonvulsants may be needed.

Antihistamines^{120,121}

Cyclizine (Cyclivert OTC), dimenhydrinate (Dramamine OTC), diphenhydramine (Benadryl), and meclizine (Antivert, Bonine) may enhance the toxic effects of CNS depressants and anticholinergics. Diphenhydramine (Benadryl) moderately inhibits CYP2D6 therefore therapy with tramadol, codeine, tamoxifen, and nebivolol should be monitored.

Anticholinergics¹²²

The absorption of oral medications may be decreased during the concurrent use of scopolamine (Transderm-Scop) because of decreased gastric motility and delayed gastric emptying. Scopolamine should be used with care in patients taking other drugs that are capable of causing CNS effects such as sedatives, tranquilizers, or alcohol. Special attention should be paid to potential interactions with drugs having anticholinergic properties; e.g., other belladonna alkaloids, antihistamines (including meclizine), tricyclic antidepressants, and muscle relaxants.

ADVERSE EFFECTS

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
NK₁ receptor antagonist								
aprepitant (Emend) ¹²³	3-6	>0.5	5-13.2	nr	0.5-5.7	7.6-10.3	4.7-17.8	5.8-12.7
fosaprepitant dimeglumine (Emend for injection) ¹²⁴	1.1-2.8	nr	2.2	<1	nr	1.1	1.4-2.9	<1
5-HT₃ antagonists								
dolasetron (Anzemet) ^{125, 126}	<1	2.2-3	7-22.9	nr	<2-5.3	2.1-5.3	2.6-5.7	nr
granisetron (Granisol) ^{127, 128}	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 transdermal (Sancuso) ¹²⁹	reported	nr	<1	nr	reported	reported*	nr	reported
ondansetron (Zofran, Zuplenz) ^{130, 131, 132}	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) ¹³³	<1	1	9	<1	1	1	<1	nr
Cannabinoids								
dronabinol (Marinol) ¹³⁴	<1	>1	<1	3-10	0.3-1	0.3-1	nr	3-10
nabilone (Cesamet) ¹³⁵	nr	reported	6-7	11-38	8	reported	reported	4

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.

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

Adverse Effects (continued)

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
Antidopaminergics^{136,137}								
metoclopramide (Reglan) ¹³⁸	reported	reported	reported	nr	reported	reported	10	reported
metoclopramide (Metozolv ODT) ¹³⁹	reported	reported	5.2	nr	reported	reported	2.1	4.2
Other^{140,141}								
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.

Antivertigo Agents ^{142,143}	Drowsiness	Xerostomia	Tachycardia	Rash	Blurred Vision	Urinary Retention
Antihistamines						
cyclizine (Cyclivert OTC)	reported	reported	reported	nr	reported	reported
dimenhydrinate (Dramamine OTC)	reported	reported	reported	reported	reported	reported
diphenhydramine (Benadryl)	reported	reported	reported	reported	reported	reported
meclizine (Antivert, Bonine, Univert)	31	16.7	reported	nr	reported	reported

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 (continued)

Antivertigo Agents^{144,145}	Drowsiness	Xerostomia	Tachycardia	Rash	Blurred Vision	Urinary Retention
Phenothiazines						
promethazine (Phenergan)	reported	reported	reported	nr	reported	reported
prochlorperazine (Compro)	reported	reported	reported	nr	reported	reported
Anticholinergics						
scopolamine (Transderm-Scop)	17	67	reported	reported	reported	reported

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.

SPECIAL POPULATIONS

Pediatrics

Prescribing information states that oral ondansetron (Zofran) can be used for patients older than four years old. However, little information is available about oral ondansetron dosing in pediatric patients four years of age or younger. There is no experience with the use of oral ondansetron 24 mg dosage in pediatric patients. There is no experience with the use of oral ondansetron in the prevention of radiation-induced or post-operative nausea and vomiting in pediatric patients.¹⁴⁶

Information is lacking regarding the use of injectable ondansetron (Zofran) in surgical patients younger than one month of age and use in cancer patients younger than six months of age.¹⁴⁷ 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 ages four years and older.¹⁴⁸ Otherwise, the safety and effectiveness of this product in children have not been evaluated.

Dolasetron (Anzemet) tablets are indicated for use in patients two years of age and older in the prevention of post-operative N/V and the prevention of chemotherapy-induced N/V. Dolasetron injection is contraindicated in pediatric patients for the prevention of N/V related to initial and repeat courses of emetogenic chemotherapy. Safety and effectiveness of injectable dolasetron in pediatric patients (two years and older) for prevention and treatment of post-operative N/V is based on pharmacokinetic studies and efficacy data in adults. Safety and effectiveness of injectable dolasetron in pediatric patients less than two years of age have not been established.

Safety and efficacy of granisetron (Granisol) and granisetron transdermal (Sancuso) have not been established for pediatric patients.^{149,150} Granisetron injectable may be used for chemotherapy-induced N/V in pediatric patients two to 16 years of age.¹⁵¹ Granisetron may be effective in patients older than four years old, according to limited randomized, controlled trials for post-operative N/V.^{152,153,154} There is no experience with oral granisetron in the prevention of radiation-induced N/V in pediatric patients.

Safety and effectiveness of use of palonosetron (Aloxi) in patients less than the age of 18 years have not been established.¹⁵⁵

Aprepitant and fosaprepitant (Emend) have not been studied in patients less than 18 years old.^{156,157} Neither dronabinol (Marinol) nor nabilone (Cesamet) have been studied in children.^{158,159} 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.¹⁶⁰

Trimethobenzamide (Tigan) injection is contraindicated in pediatric patients.¹⁶¹

Cyclizine (Cyclivert OTC), dimenhydrinate (Dramamine OTC), and diphenhydramine (Benadryl) have been used to prevent and treat N/V associated with motion sickness in pediatric populations. **Use of meclizine (Antivert, Bonine, Univert) in children less than 12 years of age is not recommended.**

Promethazine (Phenergan) and prochlorperazine (Compro) should not be used in pediatric patients less than two years of age. Safety and effectiveness of Transderm-Scop in children have not been established.

dolasetron (Anzemet) and ondansetron (Zofran)

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.¹⁶² Children were assigned randomly to one of three 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 one-hour period after the operation, there were no differences between the groups. During the period one to 24 hours after surgery, dolasetron was significantly better than placebo (16 versus 48 percent for nausea and vomiting, respectively). Over the entire 24 hours, both dolasetron and ondansetron were significantly better than placebo (32 versus 48 versus 78 percent, respectively, for nausea and vomiting). There were no significant differences between dolasetron and ondansetron, and no important adverse events were reported.

Pregnancy^{163,164,165,166,167,168,169,170,171,172,173}

The NK-1 receptor antagonist, aprepitant (Emend), is Pregnancy Category B. The 5-HT₃ antagonists, ondansetron (Zofran, Zuplenz), granisetron (Granisol), dolasetron (Anzemet), and palonosetron (Aloxi) are Pregnancy Category B. Metoclopramide (Reglan, Metozolv ODT) is Pregnancy Category B.

The cannabinoids, dronabinol (Marinol) and nabilone (Cesamet), are Pregnancy Category C. Trimethobenzamide (Tigan), promethazine (Phenergan), prochlorperazine (Compro), and scopolamine (Transderm-Scop) are Pregnancy Category C.

Geriatrics^{174,175}

Dronabinol (Marinol) 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.

Dolasetron (Anzemet) injectable is contraindicated in geriatric patients for prevention of N/V associated with initial and repeat courses of emetogenic cancer chemotherapy.

DOSAGES

Antiemetic 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 antagonist						
aprepitant (Emend)¹⁷⁶	125 mg one hour prior to chemotherapy day one, then 80 mg once daily in the morning on days two and three as part of regimen including corticosteroid and a 5-HT ₃ antagonist	--	--	40 mg within three hours prior to induction of anesthesia	--	capsules: 40, 80, 125 mg bi-pack: two 80 mg capsules tri-fold pack: one 125 mg capsule and two 80 mg capsules
fosaprepitant dimeglumine (Emend)¹⁷⁷	Single Dose regimen for Highly Emetogenic Chemotherapy (HEC) – 150 mg on day one 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 Three day dosing regimen for HEC & MEC – 115 mg on day one as an infusion over 15 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid and a 5-HT ₃ antagonist. Oral Emend 80 mg capsules are administered daily on days two and three.	--	--	--	--	injection: 115 mg per vial 150 mg per vial

Dosages (continued)

Antiemetic 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)¹⁷⁸	100 mg orally within one hour before chemotherapy	two to 16 years: 1.8 mg/kg (up to 100 mg) orally within one hour before chemotherapy Anzemet Injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients.	--	100 mg orally within two hours before surgery 12.5 mg IV given 15 minutes before the cessation of anesthesia (prevention) or as soon as N/V presents (treatment)	two to 16 years: 1.2 mg/kg orally (up to 100 mg) given within two hours before surgery. two to 16 years: 0.35 mg/kg IV (up to 12.5 mg IV) given 15 minutes before the cessation of anesthesia or as soon as N/V presents. ANZEMET Injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients. The recommended oral dose for ages two to 16 years old is 1.2 mg/kg up to 100 mg within two hours before surgery.	tablets: 50, 100 mg injection: 12.5 mg per 0.625 mL 100 mg per 5 mL 500 mg per 25 mL

Dosages (continued)

Antiemetic 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	
granisetron transdermal (Sancuso) ¹⁷⁹	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 seven days.	--	--	--	--	transdermal patch containing 34.3 mg granisetron that releases 3.1 mg over 24 hours for seven days
granisetron (Granisol) ¹⁸⁰	Oral: 2 mg up to one hour before chemotherapy for one dose OR 1 mg up to one 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: two to 16 years: 10 mcg/kg	2 mg once daily taken within one 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 oral solution: 1 mg/5 mL injection: 0.1 mg per mL, 1 mg per mL (single use vials), 4mg/4mL (multi-use vials)

Dosages (continued)

Antiemetic 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	
ondansetron (Zofran, Zuplenz) ^{181,182,183}	<p>High emetogenicity: 24 mg (three 8mg tabs) given 30 minutes before start of chemotherapy;</p> <p>Moderate emetogenicity: 8 mg given 30 minutes before start of chemotherapy with a subsequent dose eight hours after the first dose. 8 mg should then be given every 12 hours for one to two days following completion of chemotherapy.</p> <p>Injection: 0.15 mg/kg IV for three doses up to a maximum of 16 mg per dose. 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 four and eight hours after the first dose.</p>	<p>High emetogenicity: No experience with 24 mg dosage</p> <p>Moderate emetogenicity: four-11 years: 4 mg given 30 minutes before chemotherapy with subsequent doses four and eight hours after the first dose. 4 mg should be given every eight hours for one to two days after completion of chemotherapy. ≥12 years: same as adult.</p> <p>Injection: Six months – 18 years: 0.15 mg/kg IV for three doses up to a maximum of 16 mg per dose. The first dose is given 30 minutes prior to moderately to highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg IV up to a maximum of 16 mg per dose) are administered four and eight hours after the first dose. The drug should be infused over 15 minutes.</p>	8 mg up to two hours before radiation and up to three times daily for one to two days	<p>16 mg (two-8mg tabs) one hour before induction of anesthesia</p> <p>4 mg IV over two to five minutes, immediately before induction of anesthesia or postoperatively if the patient did not receive prophylactic antiemetics and has N/V within two hours after surgery.</p>	<p>One month to 12 years: <40 kg: 0.1 mg/kg IV over two to five minutes</p> <p>> 40 kg: 4 mg IV over two to five minutes immediately prior to or following anesthesia induction or postoperatively if the patient did not receive prophylactic antiemetics and has N/V shortly after surgery.</p>	<p>tablets: 4, 8, 24 mg</p> <p>oral soluble film (Zuplenz): 4, 8 mg</p> <p>oral solution: 4 mg/5 mL</p> <p>tablets, orally disintegrating (ODT): 4, 8 mg</p> <p>injection: 2 mg per mL</p> <p>solution for injection: 32 mg/50 mL in 5% dextrose, 32 mg/50 mL in 0.9% sodium chloride</p>

Dosages (continued)

Antiemetic 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	
palonosetron (Aloxi IV) ¹⁸⁴	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 (single use vial): 0.25 mg per 5 mL
Cannabinoids						
dronabinol (Marinol) ¹⁸⁵	Initial dose of 5 mg/m ² given one to three hours prior to chemotherapy, then every two to four hours after chemotherapy for a total of four to six doses per day. The initial starting dose may be adjusted in increments of 2.5 mg/m ² if necessary up to a maximum of 15 mg/m ² (per dose).	--	--	--	--	capsules: 2.5, 5, 10 mg
nabilone (Cesamet) ¹⁸⁶	Usual adult dose is 1 to 2 mg twice daily. 1 or 2 mg may be given the night prior to chemotherapy or one to three hours before initial chemotherapy. Maximum daily dose of 6 mg in divided doses (three times a day). The medication may be administered two or three 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)

Antiemetic 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 ^{187,188,189,190}						
metoclopramide (Reglan, Metozolv ODT)	1 to 2 mg/kg IV 30 minutes before chemotherapy and repeated every two hours for two doses, then every three hours for three doses	--	<p>Relief of symptomatic GERD – 10 to 15 mg orally up to four times daily at least 30 minutes prior to eating and at bedtime for up to 12 weeks</p> <p>Relief of symptoms associated with diabetic gastroparesis – 10 mg IV, IM or orally four times daily at least 30 minutes prior to eating and at bedtime for two to eight weeks. Therapy should not exceed 12 weeks.</p> <p>Facilitation of intestinal intubation or as a diagnostic aid in gastrointestinal radiography- 10 mg IV in a single dose</p>	10-20 mg IM or IV near the end of surgery. Repeat every four to six hours as necessary. If required, a 20 mg dose may be used.	--	<p>Tablets: 5, 10 mg</p> <p>Orally disintegrating tablets: 5, 10 mg</p> <p>Solution: 5 mg/5 mL</p> <p>Injection: 5 mg per mL</p>

Dosages (continued)

Antiemetic 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 ^{191,192,193,194}						
trimethobenzamide (Tigan) ¹⁹⁵	--	--	Nausea and vomiting - 250 or 300 mg capsule: three to four times daily or 200mg IM three to four times daily <i>*The suppository formulation has not been proven effective for nausea and vomiting.</i>	--	--	injection: 100 mg per mL capsules: 250, 300 mg suppository: 200 mg
phosphorated carbohydrate solution (Emetrol OTC) ¹⁹⁶	--	--	Relief of upset stomach associated with nausea: ages two to <12 years: 1-2 teaspoons age >12 years: 1-2 tablespoons May repeat dose every 15 minutes or until distress subsides. Should not be taken for more than one hour (5 doses)	--	--	3.74 g Total sugar+ 21.5 mg phosphoric acid per 5 mL

Dosages (continued)

Antivertigo Agents ^{197,198}	Adult	Pediatric	Availability
Antihistamines			
cyclizine (Cyclivert OTC)	Adults and children 12 years and older: one tablet (50 mg) every four to six hours. Do not exceed 200 mg in 24 hours.	Ages six to 11 years: ½ tablet (25 mg) every six to eight hours (Do not exceed 75 mg in 24 hours)	Tablets: 25, 50 mg Chewable Tablets: 25 mg
dimenhydrinate (Dramamine OTC, Motion Sickness OTC)	Adults and children 12 years and older: Oral: one to two tablets every four to six hours (Do not exceed eight tablets in 24 hours) Injection: 50 to 100 mg IM or IV every four hours (Do not exceed 300 mg in 24 hours)	Children ages six to 12 years: Oral: ½ to one tablet every six to eight hours (Do not exceed three tablets in 24 hours) Oral: Children ages two to six years: ¼ to ½ tablet every six to eight hours (Do not exceed more than one and one-half tablets in 24 hours) Injection: Children ages two to 12 years: 1.25 mg/kg or 37.5 mg/m² BSA IM or IV every six hours (Do not exceed 300 mg in 24 hours)	Tablets: 50 mg Chewable tablets: 50 mg Injection: 50 mg per mL
diphenhydramine (Benadryl)	Injection: 10 mg IV or IM initially then 20 to 50 mg every two to three hours as needed. Do not exceed 400mg in 24 hours. Oral: 25 to 50 mg every four to six hours in adults and children ages 12 years and older. Do not to exceed 300 mg in 24 hours.	Injection: Ages six to twelve years: 1 to 1.5 mg per kg IV or IM every six hours, not to exceed 300 mg per day. Oral: Ages six to twelve years: 12.5mg to 25 mg every four to six hours (Do not exceed 150 mg in 24 hours) Oral and Injection: Ages less than six years: safety and efficacy have not been established.	Tablets: 25, 50 mg Capsules: 25, 50 mg Chewable tablet: 25 mg Injection: 50 mg per mL Oral dissolving film: 12.5, 25 mg Oral dissolving tablet: 12.5, 25 mg Oral solution: 12.5 mg per 5 mL, 25 mg per mL
meclizine (Antivert, Dramamine Less Drowsy OTC, Bonine, Univert)	Motion Sickness: Adults and children 12 years and older (OTC Dramamine Less Drowsy): 25 to 50 mg taken one hour prior to travel. May repeat dose every 24 hours as needed. Vertigo: Adults and children 12 years and older: 25 to 100 mg daily in divided doses	--	Chewable Tablets: 25 mg Tablets: 12.5, 25, 50 mg

Dosages (continued)

Antivertigo Agents ^{199,200}	Adult	Pediatric	Availability
Phenothiazines			
promethazine (Phenergan)	Motion Sickness: Adults: 25 mg (oral or rectal) 30 to 60 minutes prior to departure, then every 12 hours as needed N/V: Adults: 12.5 to 25 (oral, rectal, IV, IM) mg every four to six hours as needed	Motion Sickness: Children over two years of age: 12.5 to 25 mg (oral or rectal) twice daily as needed with first dose given 30 to 60 minutes prior to departure N/V: Children over two years of age: 0.5 mg per pound (oral or rectal), max 25 mg per dose, every four to six hours as needed Children over two years of age: 6.25 to 12.5 mg (IM or IV) every four to six hours as needed (maximum dose: 25mg/dose)	Tablets: 12.5, 25, 50 mg Oral solution: 6.25 mg per 5 mL Suppositories: 12.5, 25, 50 mg Injection: 25 mg per mL, 50 mg per mL
prochlorperazine (Compro)	Immediate release tablets: 5 to 10 mg three to four times daily Sustained release capsules: 10 or 15 mg every 12 hours Rectal suppositories: 25 mg twice daily IV or IM: 5 to 10 mg repeated every three to four hours as needed (max dose is 40 mg/day)	Oral or rectal: Children two to 12 years (weight 18 to 39 kg): 2.5 mg three times per day or 5 mg twice per day (max: 15 mg/day). Children two to 12 years (weight 14 to 17 kg): 2.5 mg two to three times per day (max: 10 mg/day). Children two to 12 years (weight 9 to 13 kg): 2.5 mg once or twice per day (max: 7.5 mg/day). Children < two years of age and infants (weight < 9 kg): Dosage not established. IV or IM: Children two to 12 years (weight 18 to 39 kg): 0.132 mg per kg deep IM injection given three to four times per day, not to exceed 10 mg per day on the first day of treatment (max: 15 mg per day on subsequent days). Children two to 12 years (weight 14 to 17 kg): 0.132 mg per kg deep IM injection given three to four times per day (max: 10 mg per day). Children two to 12 years (weight 9 to 13 kg): 0.132 mg per kg deep IM injection given three to four times per day (max: 7.5 mg per day). Children < two years and infants (weight < 9 kg): Dosage not established.	Tablets, immediate-release: 5, 10 mg Suppositories: 25 mg Injection: 5 mg per mL

Dosages (continued)

Antivertigo Agents ^{201,202}	Adult	Pediatric	Availability
Anticholinergics			
scopolamine (Transderm-Scop)	N/V: SC injection: 0.6 to 1 mg Motion sickness: Transdermal: one disc applied behind the ear four hours prior to antiemetic need. Disc may stay in place for up to three days. If repeat dose needed, apply to skin behind opposite ear. Oral: 250 to 800 mcg one hour prior to need for antiemetic	N/V: SC injection: 0.006 mg per kg	Tablets: 0.4 mg Injection: 0.4 mg per mL Transdermal: 1.5 mg per 72 hours (delivers 1 mg over 72 hours)

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 percent 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.

Antivertigo agents used in the prevention and treatment of N/V associated with motion sickness are included in this review. There is a paucity of clinical trial data available related to motion sickness, and the primary treatment option for this condition involves the use of older medications including the more sedating antihistamines. No clinical trials are included at this time related to vertigo and motion sickness prophylaxis and treatment.

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

Patients receiving cisplatin were blindly assigned to receive one of the following three regimens: (1) aprepitant 375 mg one hour before cisplatin on day 1 and aprepitant 250 mg on days 2-5 (n=35); (2) aprepitant 125 mg before cisplatin and aprepitant 80 mg on days 2-5 (n=81); or (3) placebo before cisplatin on days 2-5 (n=86).²⁰³ All groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin, and dexamethasone 8 mg on days 2-5. The primary endpoint was complete response (no emesis and no rescue therapy) over five days following cisplatin in up to six cycles. The aprepitant 375/250 mg regimen was discontinued early in light of new pharmacokinetic data. In the first cycle, 64 percent of patients in the aprepitant group and 49 percent in the standard therapy group had a complete response (p<0.05). Thereafter, complete response rates for the aprepitant group were still 59 percent by cycle 6, but decreased to 34 percent 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.²⁰⁴ 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 complete response (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 analog 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, sixty completed the study and were available for analysis. Twenty five (42 percent) of the patients achieved CR with aprepitant while eight (13 percent) achieved CR in the placebo group ($p < 0.001$) during days 1 through 8. Of the 25 patients that received CR with aprepitant, seven received CR when they crossed over to the placebo arm and of the eight patients that received CR on placebo, seven received CR when they crossed over to aprepitant. Twenty eight (47 percent) of the patients in the aprepitant group achieved a CR in the acute phase compared with nine (15 percent) in the placebo group ($p < 0.001$). Thirty eight patients (63 percent) in the aprepitant group achieved a CR in the delayed phase compared to 21 (42 percent) of the patients in the placebo group ($p < 0.001$).

aprepitant (Emend) versus ondansetron (Zofran)

Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study.²⁰⁵ Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) one to three 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 percent in the aprepitant group and 38 percent in the ondansetron group ($p = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at two hours (six percent versus 21 percent, $p = 0.0419$) and 24 hours (14 percent versus 36 percent, $p = 0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69 versus 60 percent), nausea scores, need for rescue antiemetics (65 versus 60 percent), complete response [no post-operative nausea and vomiting (PONV) and no rescue, 22 versus 36 percent], 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 complete response 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 post-operative nausea and vomiting and severity of nausea for up to 48 hours in 150 adult patients undergoing plastic surgery.²⁰⁶ Patients were randomized to take 40 mg of oral aprepitant plus 4 mg intravenous ondansetron (Group A, $n = 75$) or oral placebo plus 4 mg intravenous ondansetron (Group B, $n = 75$). Oral aprepitant or placebo was given to patients two hours prior to their scheduled operation. All patients in both groups received the same anesthetic regimen and 4 mg of intravenous 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 percent) experienced less vomiting than those in Group B (29.7 percent, $p=0.003$), indicating a relative risk reduction of 31.3 percent (95% CI). 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 percent in Group A and 44.6 percent in Group B) or complete response (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)

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 moderately emetogenic chemotherapy.²⁰⁷ Single oral doses of 25, 50, 100, or 200 mg of dolasetron were administered one 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. Complete response rates were 45, 49.4, 60.5, and 76.3 percent for 25, 50, 100, and 200 mg dolasetron, respectively, and 72.3 percent 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 percent 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 moderately emetogenic chemotherapy.

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.²⁰⁸ In addition to dexamethasone 10 mg IV, 102 patients were randomized to receive either ondansetron 8 mg orally every eight hours, granisetron 1 mg orally every 12 hours, or ondansetron 32 mg IV every 24 hours, each given on days one and two. Overall complete response rates were 48 percent for oral ondansetron, 47 percent for oral granisetron, and 49 percent for IV ondansetron; this difference is not statistically significant ($p=NS$). Overall major efficacy rates were 82 percent for oral ondansetron, 84 percent for oral granisetron, and 81 percent for IV ondansetron ($p=NS$). Mean visual analog scale (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 two cycles of identical chemotherapy over five days.²⁰⁹ Primary efficacy variables were prospectively defined as complete response (no vomiting and mild or absent nausea) over five days and patient preference. Both agents achieved good control of emetic symptoms

with five-day complete response rates of 44 percent on granisetron and 39.8 percent on ondansetron ($p=NS$). Complete response rates were very similar in patients receiving either cisplatin or ifosfamide. There was a statistically significant difference in patient preference in favor of granisetron ($p=0.048$).

A randomized, cross-over pilot study of post-operative nausea and vomiting (PONV) was conducted in 250 female patients who received prophylactic ondansetron 4 mg at the end of a surgical procedure requiring general anesthesia.²¹⁰ Women were then followed post-operatively for four hours. Eighty-eight of the women developed PONV and were randomly assigned to receive one 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 complete response of 57 percent, those receiving granisetron 1 mg or 0.1 mg had complete responses of 60 percent and 68 percent, 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.²¹¹ 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) one hour before induction of anesthesia. Post-operative N/V was assessed until 24 hours post surgery. A complete response in zero to two hours after anesthesia was found in 43 percent, 63 percent, and 90 percent of patients who had received placebo, granisetron, or ondansetron, respectively; and of these, the percentages of patients requiring rescue antiemetics were 40 percent, 17 percent, and seven percent. The presence of N/V was less than 23 percent after two hours in all three groups. In addition, after two hours, N/V scores and need for antiemetics were similar in all three groups. Oral ondansetron 4 mg provided better preemptive antiemesis than oral granisetron 2 mg and placebo in the two hours following surgery with general anesthesia.

granisetron versus granisetron transdermal (Sancuso)

A Phase III, 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.²¹² 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 percent of patients and in 64.8 percent of the patients taking granisetron orally ($p=NS$).

granisetron versus palonosetron (Aloxi) for injection

A Phase III, multicenter, randomized, double-blind, double-dummy, stratified, parallel-group, active-comparator trial was conducted in 1,143 Japanese patients with cancer who received multi-day, highly emetogenic cancer chemotherapy (HEC) to compare the efficacy and safety of palonosetron versus granisetron for chemotherapy-induced N/V (CINV) with coadministration of dexamethasone.²¹³ HEC consisted of cisplatin or an anthracycline and cyclophosphamide combination (AC/EC). Patients were randomized to receive either single-dose palonosetron 0.75 mg or granisetron 40 mcg/kg on day one 30 minutes prior to the start of chemotherapy. Also, on day one, patients received dexamethasone 16 mg IV followed by an additional 8 mg IV for patients receiving IV cisplatin or 4 mg orally for patients receiving AC/EC on days two and three. The primary endpoints were the proportion of patients with a

complete response (defined as no emetic episodes and no rescue medication) during the acute phase (zero to 24 hours after chemotherapy – considered a non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24 to 120 hours after chemotherapy – superiority comparison with granisetron). Approximately 1,114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. Of the 555 patients treated with palonosetron, 418 (75.3 percent) had a complete response during the acute phase compared with 410 of the 559 patients (73.3 percent) treated with granisetron [mean difference of 2.9 percent, 95% CI, -2.7 to 7.27]. During the delayed phase, 315 of 555 patients (56.8 percent) had a complete response in the palonosetron group compared with 249 of 559 patients (44.5 percent) in the granisetron group ($p < 0.0001$). According to the authors, when administered with dexamethasone prior to HEC, palonosetron is non-inferior to granisetron in the acute phase and superior in the delayed phase. There is a comparable safety profile for both treatments.

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.²¹⁴ Patients at least eighteen 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 one 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 20 mg IV plus aprepitant 125 mg orally on day 1 with aprepitant 80 mg orally and dexamethasone 8 mg orally on day 2 and placebo on day 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 day two and prochlorperazine 10 mg on day three (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 four time intervals per day (morning, afternoon, evening, and night) and was rated using a seven 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).

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

A five-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 chemotherapy-induced nausea and vomiting (CINV).²¹⁵ Patients receiving moderately to highly emetogenic chemotherapy received dexamethasone 20 mg orally, ondansetron 16 mg IV, and either placebo or dronabinol 2.5 mg pre-chemotherapy on day one. Patients randomized to active treatment (dronabinol and/or ondansetron) also received dronabinol 2.5 mg after chemotherapy on day one. On day two, fixed doses of placebo, dronabinol 10 mg, ondansetron 16 mg, or combination therapy were administered. On days three to five, 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 percent), ondansetron (58 percent), and combination (47 percent) versus placebo (20 percent). Nausea absence was significantly greater for the active treatment groups versus placebo (15 percent): dronabinol (71 percent), ondansetron (64 percent), and combination (53 percent, $p < 0.05$ 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.

orally disintegrating ondansetron (Zofran ODT) versus conventional tablet formulation of ondansetron (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.²¹⁶ In a randomized trial, 134 patients received ondansetron ODT 8 mg twice daily or ondansetron tablet 8 mg twice daily, both for three days. Ondansetron tablet was significantly better at controlling emesis (72 percent versus 52 percent, respectively, $p = 0.020$) and statistically insignificant when attempting to control nausea (66 percent versus 48 percent, respectively, $p = 0.054$) compared to ondansetron ODT. However, when looking at major control of emesis (as having zero to two emetic episodes during the three days) between the conventional ondansetron tablet versus ondansetron ODT, there was no real difference (76 percent versus 70 percent, respectively, $p = 0.28$). For control of major emesis and nausea, there are no major differences between the formulations.

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 post-operative N/V.²¹⁷ Patients received either an active transdermal scopolamine patch or a placebo patch two 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, 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 percent for the combination group and 39 percent 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 percent versus 25 percent, $p < 0.01$). The time to first nausea, vomiting/retching, or rescue episode was statistically significantly longer for the combination group compared with the ondansetron-only group ($p < 0.05$).

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.²¹⁸ Nausea was evaluated on a 100-mm visual analog scale (VAS) at baseline and then 30 minutes after treatment. Patients who have a VAS score of 40-mm or more were randomized to receive intravenous 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 percent were female. The median VAS reductions (95% CI) 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.

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 zero to two hours and two to 24 hours post-operation.²¹⁹ 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 two 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 zero to two hours post-operation there were no significant differences in the incidence of nausea and vomiting between the ondansetron and palonosetron groups. However, from two 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 percent versus 28 percent, respectively, during the two 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 percent versus 62 percent, $p = 0.045$). 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 intravenous ondansetron two to 24 hours post-operation for patients at high risk for post-operative nausea and vomiting.

SUMMARY

The 5-HT₃ antagonists offer significant advantages in the prevention of N/V due to chemotherapy and radiotherapy. Based on available data, there appears to be little significant difference among the drugs in this class. All of the available antiemesis guidelines reflect this stance. However, expert guidelines now differ on this conclusion with the ASCO and NCCN now suggesting palonosetron (Aloxi) demonstrates superiority in preventing emesis due to high or moderate risk chemotherapy agents and MASCC concluding the studies were flawed and additional research is needed to accurately determine superiority. 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 (Granisol). The ondansetron oral soluble film (Zuplenz) has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron (Zofran ODT).

Aprepitant (Emend) 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, but its effectiveness has not been compared to other agents for these uses.

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.

There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications used including antihistamines, phenothiazines and anticholinergics typically cause drowsiness or similar adverse effects.

REFERENCES

- 1 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 2 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 3 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 4 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 5 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
- 6 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 7 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2011.
- 8 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 9 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 10 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 11 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 12 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 13 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 14 Available at: www.drugs.com. Accessed January 28, 2013.
- 15 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 16 Reglan [package insert]. Baudette, MN; Ani; August 2011.
- 17 Metozolv ODT [package insert]. Morrisville, NC; Salix Pharmaceuticals; December 2011.
- 18 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 19 Available at: www.drugs.com. Accessed January 28, 2013.
- 20 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 21 Available at: www.drugs.com. Accessed January 28, 2013.
- 22 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 23 Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 28, 2013.
- 24 Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 28, 2013.
- 25 Kris MG, Hesketh PJ, Somerfield MR et al. American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. J Clin Oncol. 2006; 24(18):2932-2947. Available at: <http://jco.ascopubs.org/content/24/18/2932.full>. Accessed January 28, 2013.

- 26 Gralla RJ, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin. Onc.* 1999; 17(9): 2971. Available at: <http://jco.ascopubs.org/content/17/9/2971.full>. Accessed January 28, 2013.
- 27 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.
- 28 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).
- 29 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.
- 30 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).
- 31 Gralla RJ, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin. Onc.* Vol 17, Issue 9 (September), 1999: 2971.
- 32 Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 28, 2013.
- 33 Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 28, 2013.
- 34 American Gastroenterological Association. Medical position statement: Nausea and vomiting. *Gastroenterology.* 2011; 29(31):4189-4198.
- 35 Kris MG, Hesketh PJ, Somerfield MR et al. American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. *J Clin Oncol.* 2006; 24(18):2932-2947. Available at: <http://jco.ascopubs.org/content/24/18/2932.full>. Accessed January 28, 2013.
- 36 Available at: <http://www.mascc.org/mc/page.do?sitePageId=88041>. Accessed January 28, 2013.
- 37 American Society of Health-System Pharmacists. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *Am J Health-Syst Pharm.* 1999; 56:729-764.
- 38 Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 28, 2013.
- 39 Kris MG, Hesketh PJ, Somerfield MR et al. American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2011. *J Clin Oncol.* 2011; 29(31):4189-4198. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3219469/>. Accessed January 28, 2013.
- 40 Available at: <http://www.asco.org/>. Accessed January 28, 2013.
- 41 Available at: <http://www.mascc.org/mc/page.do?sitePageId=88041>. Accessed January 28, 2013.
- 42 Available at: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed January 28, 2013.
- 43 Available at: <http://www.mascc.org/mc/page.do?sitePageId=88041>. Accessed January 28, 2013.
- 44 Kris MG, Hesketh PJ, Somerfield MR et al. American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. *J Clin Oncol.* 2006; 24(18):2932-2947. Available at: <http://jco.ascopubs.org/content/24/18/2932.full>. Accessed January 28, 2013.
- 45 Available at: <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/motion-sickness.aspx>. Accessed January 28, 2013.
- 46 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 47 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 48 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.
- 49 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 50 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 51 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 52 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 53 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 54 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 55 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 56 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 57 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 58 Meller D, Vincent M. The emerging role of cannabinoid neuromodulators in symptom management. *Support Care Cancer.* 2007; 15: 63–71.
- 59 Available at: www.drugs.com. Accessed January 28, 2013.
- 60 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 61 Metozolv ODT [package insert]. Morrisville, NC; Salix Pharmaceuticals; December 2011.
- 62 Available at: www.drugs.com. Accessed January 28, 2013.
- 63 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 64 Available at: www.drugs.com. Accessed January 28, 2013.
- 65 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 66 Available at: www.drugs.com. Accessed January 28, 2013.
- 67 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 68 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 69 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 70 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 71 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 72 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
- 73 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 74 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2011.
- 75 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2011.
- 76 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 77 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2012.
- 78 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 79 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 80 Cesamet [package insert]. Costa Mesa, CA; Valeant; December 2008.
- 81 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.

- 82 Available at: www.drugs.com. Accessed January 28, 2013.
- 83 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 84 Metozolv ODT [package insert]. Morrisville, NC; Salix Pharmaceuticals; December 2011.
- 85 Available at: www.drugs.com. Accessed January 28, 2013.
- 86 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 87 Available at: www.drugs.com. Accessed January 28, 2013.
- 88 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 89 Anzemet tablets [package insert]. Kansas City, MO; Aventis Pharmaceuticals; September 2011.
- 90 Granisol [package insert]. Madison, MS; PediatRx November 2010.
- 91 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 92 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2011.
- 93 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 94 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 95 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 96 Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149533.htm>. Accessed January 28, 2013.
- 97 Available at: www.drugs.com. Accessed January 28, 2013.
- 98 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 99 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 100 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 101 Tigan [package insert]. Rochester, MI; JHP Pharmaceuticals, LLC.; February 2009.
- 102 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 103 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 104 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.
- 105 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 106 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 107 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
- 108 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 109 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2011.
- 110 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 111 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 112 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2012.
- 113 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 114 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 115 Available at: www.drugs.com. Accessed January 28, 2013.
- 116 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 117 Metozolv ODT [package insert]. Morrisville, NC; Salix Pharmaceuticals; December 2011.
- 118 Available at: www.drugs.com. Accessed January 28, 2013.
- 119 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 120 Available at: www.drugs.com. Accessed January 28, 2013.
- 121 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 122 Transderm Scop [package insert]. Parsippany, NJ; Novartis Consumer Health. February 2006.
- 123 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 124 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co. July 2012.
- 125 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 126 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 127 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
- 128 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 129 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2011.
- 130 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2011.
- 131 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 132 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2012.
- 133 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 134 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 135 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 136 Available at: www.drugs.com. Accessed January 28, 2013.
- 137 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 138 Reglan [package insert]. Baudette, MN; Ani; August 2011.
- 139 Metozolv ODT [package insert]. Morrisville, NC; Salix Pharmaceuticals; December 2011.
- 140 Available at: www.drugs.com. Accessed January 28, 2013.
- 141 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 142 Available at: www.drugs.com. Accessed January 28, 2013.
- 143 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 144 Available at: www.drugs.com. Accessed January 28, 2013.
- 145 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 146 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 147 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2012.

- 148 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 149 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
- 150 Kytiril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 151 Kytiril [package insert]. South San Francisco, CA; Genentech USA, Inc; April 2011.
- 152 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.
- 153 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.
- 154 Fujii Y, Toyooka H, Tanaka H. Oral granisetron prevents postoperative vomiting in children. *Br J Anaesth*. 1998; 81(3):390-392.
- 155 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 156 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2012.
- 157 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co. July 2012.
- 158 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 159 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011
- 160 Reglan injection [package insert]. Deerfield, IL; Baxter Healthcare Corp; November 2010.
- 161 Tigan [package insert]. Rochester, MI; JHP Pharmaceuticals, LLC.; February 2009.
- 162 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.
- 163 Emend [package insert]. Whitehouse Station, NJ; Merck & Co. July 2012.
- 164 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 165 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 166 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
- 167 Kytiril [package insert]. South San Francisco, CA; Genentech; April 2011.
- 168 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 169 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 170 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 171 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 172 Metozolv ODT [package insert]. Morrisville, NC; Salix Pharmaceuticals; December 2011.
- 173 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 174 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 175 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 176 Emend [package insert]. Whitehouse Station, NJ; Merck & Co. July 2012.
- 177 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co. July 2012.
- 178 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S.LLC; September 2011.
- 179 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2011.
- 180 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 181 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 182 Zuplenz [package insert]. Woodcliff Lake, NJ; Par Pharmaceuticals; July 2010.
- 183 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2012.
- 184 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai, Inc; September 2008.
- 185 Marinol [package insert]. Marietta, GA; Abbott; March 2010.
- 186 Cesamet [package insert]. Costa Mesa, CA; Valeant; April 2011.
- 187 Available at: www.drugs.com. Accessed January 28, 2013.
- 188 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 189 Available at: www.drugs.com. Accessed January 28, 2013.
- 190 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 191 Available at: www.drugs.com. Accessed January 28, 2013.
- 192 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 193 Available at: www.drugs.com. Accessed January 28, 2013.
- 194 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 195 Tigan [package insert]. Rochester, MI; JHP Pharmaceuticals, LLC.; February 2009.
- 196 Available at: <http://emetrol.com/product-info.html>. Accessed September 20, 2012.
- 197 Available at: www.drugs.com. Accessed January 28, 2013.
- 198 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 199 Available at: www.drugs.com. Accessed January 28, 2013.
- 200 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 201 Available at: www.drugs.com. Accessed January 28, 2013.
- 202 Available at: www.clinicalpharmacology.com. Accessed January 28, 2013.
- 203 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.
- 204 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.
- 205 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.
- 206 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.

- 207 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.
- 208 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.
- 209 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.
- 210 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.
- 211 Bhatnagar S, Gupta D, 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.
- 212 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2011.
- 213 Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention for nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomized, comparative phase III trial. *Lancet Oncol*. 2009; 10(2):115-24.
- 214 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.
- 215 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.
- 216 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.
- 217 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.
- 218 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.
- 219 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.