Therapeutic Class Overview
Antiemetics

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (Longstreth, 2017).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (Hesketh, 2017[a], National Cancer Institute, 2017).
- The precise mechanism by which chemotherapy induces n/v remains unclear; however, it is known to involve several areas in the central and peripheral nervous systems and the GI tract. Some chemotherapy agents may interact with receptors in areas of the brainstem, leading to activation of the vomiting center. In addition, chemotherapy may cause intestinal cell damage and the release of serotonin (5-hydroxytryptamine [5-HT]), with subsequent activation of emetic reflexes. More than 30 neurotransmitters have been associated with nervous system sites involved in CINV; the most clinically relevant of these are dopamine, 5-HT, and substance P (Hesketh et al, 2016).
- Approximately one-third of surgical patients have nausea, vomiting, or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (Longstreth, 2017).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (Feyer et al, 2017).
- Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (American College of Obstetrics and Gynecologists [ACOG] 2015, Smith et al, 2017).
- The mechanism of action for the 5-HT_3 agents results from the blockade of 5-HT_3 receptors in both the gastric area and the chemoreceptor trigger zone in the central nervous system (CNS). By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (Mannix et al, 2006).
- The substance P/neurokinin 1 (NK_1) receptor antagonists cross the blood brain barrier and occupy the NK_1 receptors in the brain, leading to reduced symptoms of n/v.
- The mechanism of action of DICLEGIS® and BONJESTA® (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown; however, doxylamine is known to compete with histamine for H1-receptor sites and block the chemoreceptor trigger zone thereby decreasing n/v (Smith et al, 2017).
- The 5-HT_3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The substance P/NK_1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.
- The combination product, AKNYZEO®, contains palonosetron, a 5-HT_3 receptor antagonist, and netupitant, a substance P/NK_1 receptor antagonist. This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.
- DICLEGIS and BONJESTA are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. DICLEGIS and BONJESTA are indicated for the treatment of NVP in women who do not respond to conservative management. It should be noted that these agents have not been studied in hyperemesis gravidarum.
- The combination of doxylamine and pyridoxine was previously available in the United States under the brand name BENDECTIN®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects (Smith et al, 2017).

- Medispan Therapeutic Class: 5-HT_3 Receptor Antagonists; Substance P/NK_1 Receptor Antagonists; Antiemetic Combinations – Two Ingredient; Miscellaneous.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALOXI® (palonosetron) IV injection*	Eisai, Inc.	07/25/2003	-†
ANZEMET® (dolasetron) injection	Sanofi-Aventis U.S.	09/11/1997	-
ANZEMET (dolasetron) tablets	Sanofi-Aventis U.S.	09/11/1997	-
BONJESTA (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	Duchesnay, Inc.	11/07/2016	-
DICLEGIS (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	Duchesnay, Inc.	04/08/2013	-
granisetron injection	Various	12/29/1993 (KYTRIL®)	√‡
granisetron tablets	Various	03/16/1995 (KYTRIL)	√‡
SANCUSO® (granisetron) transdermal patch	Prostrakan, Inc.	09/12/2008	-
SUSTOL® (granisetron) extended-release injection	Heron Therapeutics	08/09/2016	-
ZOFRAN® (ondansetron) injection	GlaxoSmithKline	01/04/1991	√‡
ZOFRAN (ondansetron) tablet	GlaxoSmithKline	12/31/1992	√‡
ZOFRAN ODT® (ondansetron) orally disintegrating tablet	GlaxoSmithKline	01/27/1999	√‡
ZOFRAN (ondansetron) oral solution	GlaxoSmithKline	01/24/1997	√‡
ZUPLENZ® (ondansetron) oral soluble film	Galena Biopharma, Inc.	07/02/2010	-
EMEND® (aprepitant) capsule	Merck & Co., Inc.	03/26/2003	√
EMEND (aprepitant) oral suspension	Merck & Co., Inc.	12/17/2015	-
EMEND (fosaprepitant) injection	Merck & Co., Inc.	10/12/2010	-**
VARUBI™ (rolapitant) tablet	Tesaro, Inc.	09/01/2015	-
AKYNZEO (palonosetron/netupitant) capsule	Eisai, Inc.	10/10/2014	-

Abbrv: IV=intravenous, ODT=orally disintegrating tablet
*FDA approved ALOXI as an oral capsule on August 22, 2008, but neither Helsinn Healthcare nor Eisai have ever marketed ALOXI capsules. ALOXI oral capsules are listed on FDA's web site as "discontinued."
**Sandoz received FDA approval for generic EMEND injection on September 24, 2012. However, patents will likely protect EMEND injection from generic competition until March 4, 2019, pending patent litigation.
†Generics listed in the FDA Orange Book but are not yet marketed.
‡Generic available in at least one dosage form and/or strength.

(DRUGS@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA-Approved Indication

Indication	5-HT_3 Receptor Antagonists				Substance P/NK_1 Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
Highly emetogenic cancer chemotherapy – prevention of acute n/v associated with initial and repeat courses in adults				√					
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy								√	
Moderately emetogenic cancer chemotherapy – prevention of acute and delayed n/v associated with initial and repeat courses in adults				√					
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy in patients ≥6 months of age					√ (oral suspension)				
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including				√					

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
highly emetogenic chemo in pediatric patients aged one month to <17 years									
Prevention of acute and delayed n/v associated with initial and repeat courses of highly emetogenic cancer chemo-therapy, including high-dose cisplatin, when used in combination with other antiemetic agents						√	√		
Prevention of acute and delayed n/v associated with initial and repeat courses of highly emetogenic cancer chemo-therapy, including high-dose cisplatin, when used in combination with other antiemetic agents in patients ≥12 years of age					√ (capsule)				
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy when used in combination with other antiemetic agents							√		
Prevention of n/v associated with initial and repeat courses of						√			

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
moderately emetogenic cancer chemotherapy when used in combination with other antiemetic agents									
Prevention of n/v associated with initial and repeat courses of moderately emetogenic cancer chemotherapy when used in combination with other antiemetic agents in patients ≥12 years of age					√ (capsule)				
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been demonstrated				√					

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
Prevention of postoperative nausea and/or vomiting; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur postoperatively; in patients in whom nausea and/or vomiting must be avoided postoperatively, ZOFRAN injection is recommended even when the incidence of PONV is low; for patients who do not receive prophylactic ZOFRAN injection and experience n/v postoperatively, ZOFRAN injection may be given to prevent further episodes			√ (injection)						
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥6 months of age			√ (injection)						
Prevention of n/v associated with initial and repeat courses of moderately emetogenic cancer chemotherapy			√ (tablet, ODT, oral solution, oral soluble film)		√ (oral suspension)				
Prevention of n/v associated with highly			√ (tablet, ODT,						

Indication	5-HT_3 Receptor Antagonists				Substance P/NK_1 Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
emetogenic cancer chemotherapy including cisplatin ≥ 50 mg/m^2			oral solution, oral soluble film)						
Prevention of PONV in adults					√ (capsule)				
Prevention of PONV in adults and children two years and older; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, ANZEMET injection is recommended even where the incidence of PONV is low. Do not rechallenge a patient who has failed a previous trial of a 5-HT_3 receptor antagonist with a repeat dose of dolasetron.	√ (injection)								
Prevention of n/v in patients receiving moderately and/or highly emetogenic chemotherapy for up to five consecutive days		√ (transdermal patch)							
Prevention of n/v associated with moderately emetogenic cancer chemotherapy, including	√ (tablet)								

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
initial and repeat courses in adults and children two years and older									
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin		√ (injection, tablets)							
Prevention of n/v associated with radiation, including TBI and fractionated abdominal radiation		√ (tablets)							
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose fraction to the abdomen, or daily fractions to the abdomen			√ (tablet, ODT, oral solution, oral soluble film)						
Treatment of n/v of pregnancy in women who do not respond to conservative management									√
Treatment of postoperative nausea and/or vomiting in adults and children two years and older	√ (injection)								
Prevention of postoperative nausea and/or vomiting; as with other antiemetics, routine prophylaxis is not		√ (injection)	√ (tablet, ODT, oral solution, oral soluble film)						

Indication	5-HT_3 Receptor Antagonists				Substance P/NK_1 Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.									
Prevention of acute and delayed n/v associated with initial and repeat courses of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide combination chemotherapy regimens, in combination with other antiemetics.		√ (extended-release injection)							

Abbrv: ODT=orally disintegrating tablet, PONV=postoperative nausea and vomiting, TBI=total body irradiation

(Prescribing information: AKYNZEO, 2015; ALOXI, 2015; ANZEMET injection, 2014; ANZEMET tablets, 2014; BONJESTA, 2016; DICLEGIS tablets, 2013; EMEND capsules and oral suspension, 2017; EMEND for injection, 2016; granisetron injection, 2015; granisetron tablets, 2015; ondansetron, 2014; SANCUSO, 2015; SUSTOL, 2016; VARUBI 2015; ZOFRAN injection, 2014; ZOFRAN, tablets, ODT, oral solution, 2016; ZUPLENZ, 2017)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

CINV

- ANZEMET (dolasetron) has been shown to be an effective therapy in the treatment of CINV in comparative studies with ALOXI (palonosetron), ZOFRAN (ondansetron), and placebo (Eberhart et al, 2004; Eisenberg et al, 2003; Karamanlioglu et al, 2003; Lofters et al, 1997; Meyer et al, 2005, Walker et al, 2001).
- Granisetron and ZOFRAN (ondansetron) are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of one over another, but this has not been a consistently proven outcome (Billio et al, 2010; Dabbous et al, 2010; del Giglio et al, 2000; Dempsey et al, 2004; Gan et al, 2005; Jaing et al, 2004; Kalaycio et al, 1998; Lacerda et al, 2000; Orchard et al, 1999; White et al, 2006).
- Granisetron and ZOFRAN (ondansetron) have also been shown to be effective in the treatment of RINV (Spitzer et al, 2000; Salvo et al, 2012).
- SANCUSO (granisetron) patch was non-inferior to orally administered granisetron for CINV (Boccia et al, 2011).
- ALOXI (palonosetron) was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (Aapro et al, 2005; Billio et al, 2010; Botrel et al, 2011; Dong et al, 2011; Eisenberg et al, 2003; Gralla et al, 2003; Kaushal et al, 2010; Likun et al, 2011; Massa et al, 2009; Suzuki et al, 2016).
- The safety and efficacy of SUSTOL (granisetron ER) were evaluated in a pivotal Phase 3 double-blind, double-dummy, multicenter, randomized controlled trial in adults receiving highly emetogenic chemotherapy or moderately emetogenic chemotherapy (Raftopoulos et al, 2015[a], Raftopoulos et al, 2015[b]). In the modified intention-to-treat population, both granisetron ER 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after highly and moderately emetogenic chemotherapy. The FDA-approved dose of granisetron ER 10 mg was non-inferior to palonosetron in preventing delayed CINV after moderately emetogenic chemotherapy and was not superior in preventing delayed CINV after highly emetogenic chemotherapy (Raftopoulos et al, 2015[a], Raftopoulos et al, 2015[b]).
- All of the 5-HT_3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate meta-analyses and are superior to placebo (Billio et al, 2010; del Giglio et al, 2000; George et al, 2009; Singhal et al, 2012; Tang et al, 2012). A 2016 meta-analysis comparing ondansetron to other 5-HT_3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (Simino et al, 2016).
- A 2016 Cochrane review found that 5-HT_3 receptor antagonists are effective in children who receive emetogenic chemotherapy (Phillips et al, 2016). Granisetron or ALOXI (palonosetron) may be more effective than ZOFRAN (ondansetron), and the addition of dexamethasone improves vomiting symptoms.
- A randomized, double-blind, non-inferiority study comparing single-dose palonosetron (20 mcg/kg) to multi-dose ondansetron (150 mcg/kg x 3 doses) for the prevention of CINV in pediatric patients (0 to 17 years) receiving moderately or highly emetogenic chemotherapy found that palonosetron was non-inferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (Kovacs et al, 2016).
- A randomized, double-blind study in patients receiving highly emetogenic chemotherapy found that when used as part of combination therapy with dexamethasone and EMEND (aprepitant), intravenous palonosetron was not more efficacious than intravenous granisetron at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (Suzuki et al, 2016).
- One multicenter, double-blind, randomized controlled trial evaluated dexamethasone compared to EMEND (aprepitant) in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (i.e., no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and EMEND (aprepitant) in the prevention of delayed emesis (Roila et al, 2014).
- EMEND (aprepitant) has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT_3 antagonists and/or dexamethasone (Herrington et al, 2008; Rapoport et al, 2010; Yeo et al, 2009; Herrstedt et al, 2005; Warr et al, 2005; Gralla et al, 2005; De Wit et al, 2004; Poli-Bigelli et al, 2003; Hesketh et al, 2003; Martin et al, 2003; Gore et al, 2009; Jordan et al, 2009; Grunberg et al, 2009).
- In combination regimens with granisetron and dexamethasone, VARUBI (rolapitant) has been shown to be more effective than placebo for the prevention of CINV due to moderately and highly emetogenic chemotherapy in clinical trials (Rapoport et al, 2015; Schwartzberg et al, 2015). In combinations with 5-HT_3 antagonists and dexamethasone, addition of VARUBI (rolapitant) has also been shown to be more effective at preventing CINV

over multiple cycles of moderately or highly emetogenic chemotherapy, when compared to similar combinations without rolapitant (Rapoport et al, 2016).
- The fixed-dose combination AKYNZEO (palonosetron and netupitant) + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following moderately emetogenic chemotherapy (Aapro et al, 2014); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (Gralla et al, 2014).

PONV

- In a meta-analysis, ALOXI (palonosetron) was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ZOFRAN (ondansetron) (Xiong et al, 2015).
- A 2016 meta-analysis found that when compared to other 5-HT3 antagonists and NK_1 antagonists, EMEND (aprepitant) reduces incidence of PONV, and need for rescue medications (Singh et al, 2016).

Pregnancy
- FDA-approvals of DICLEGIS and BONJESTA were based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to 3.9 point decrease in the placebo group (P=0.006). For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the DICLEGIS group compared to a 1.8 point decrease in the placebo group (P=0.005) (Koren et al, 2010).
    - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine/pyridoxine as compared to placebo. Based on the results of this analysis, doxylamine/pyridoxine was not associated with an overall increased in rate of adverse effects as compared to placebo (Koren et al, 2015).

Guidelines
- The 5-HT_3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV (American Gastroentrological Association [AGA], 2001; Herrstedt et al, 2016; Hesketh et al, 2016; Gan et al, 2014; Gupta et al, 2016; Roila et al, 2010).
- Treatment of CINV or RINV generally involves the use of multiple agents that affect different receptor types (AGA, 2001; Herrstedt et al, 2016; Hesketh et al, 2016; Roila et al, 2010).
    - The 2016 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (Hesketh et al, 2016):
        - For the prevention of n/v induced by highly emetogenic chemotherapy agents, a three drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone is recommended as first-line therapy.
        - For moderately emetogenic agents, a two-drug combination of ALOXI (palonosetron) and dexamethasone is recommended.
        - For children receiving highly or moderately emetogenic agents, a 5-HT_3 receptor antagonist plus a corticosteroid is recommended.
    - The 2016 expert opinion statement from the American Society for Enhanced Recovery (ASER) for the prophylaxis and management of PONV provides the following recommendations (Gupta et al, 2016):
        - All patients should receive PONV prophylaxis during the perioperative period.
        - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
    - The 2015 ACOG Practice Bulletin for nausea and vomiting of pregnancy recommends the following:
        - Mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods.
        - First-line pharmacotherapy with pyridoxine or in combination with doxylamine.

- o If initial therapy with pyridoxine monotherapy is inadequate, then the addition of doxylamine is recommended.

SAFETY SUMMARY

- The Antiemetics – 5-HT_3 Receptor Antagonists and Substance P/NK_1 Receptor Antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAIO), as they intensify and prolong the adverse effects of the agent.
- EMEND is contraindicated in patients taking pimozide due to the risk of significantly increased plasma concentrations of pimozide, potentially resulting in prolongation of the QT interval. VARUBI is contraindicated in patients taking thioridazine, a CYP2D6 substrate. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and Torsades de Pointes.
- The 5-HT_3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for ANZEMET (dolasetron) regarding the risk of arrhythmias. ZOFRAN (ondansetron) and granisetron have QTc prolongation as a general precaution, but the incidence of electrocardiogram (ECG) changes has been less than 1%. In addition, the development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists.
- EMEND (aprepitant) and AKYNZEO (netupitant/palonosetron) have several potential drug interactions. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4 and CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Please see the prescribing information for specific drugs affected and additional details.
- The most common adverse effect observed with doxylamine/pyridoxine is somnolence. The warning section in the prescribing information states that activities requiring complete mental alertness, such as driving or operating heavy machinery, while using doxylamine/pyridoxine, are not recommended (unless cleared to do so by the health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties, so should be used with caution in women with asthma, increased intraocular pressure, narrow angle glaucoma, stenosis peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction.

DOSAGE AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
5-HT_3 Receptor Antagonists				
Dolasetron	Injection: 20 mg/mL vial Tablet: 50 mg 100 mg	<u>Prevention or treatment of postoperative nausea and/or vomiting:</u> Injection: 12.5 mg IV as a single dose 15 min before the cessation of anesthesia (prevention) or as soon as nausea or vomiting presents (treatment) <u>Prevention of cancer CINV:</u> Tablet: 100 mg within one hour before chemotherapy	<u>Prevention or treatment of postoperative nausea and/or vomiting:</u> Injection: 0.35 mg/kg IV, with a maximum dose of 12.5 mg, given as a single dose 15 min before the cessation of anesthesia or as soon as nausea or vomiting presents <u>Prevention of cancer CINV:</u> Tablet: 1.8 mg/kg within one hour before chemotherapy, up to a maximum of 100 mg	Dolasetron injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients. When the injection is administered orally, the oral dosage in children is 1.2 mg/kg up to a maximum 100 mg dose within two hours before surgery.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
				The prepared solution may be kept up to two hours at room temperature before use.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
Granisetron	Extended-release subcutaneous injection: 10 mg/0.4 mL per kit; supplied as cartons of six kits. Injection: 0.1 mg/mL 1 mg/mL Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours	Emetogenic chemotherapy: Tablet: two 1 mg tablets once daily up to one hour before chemotherapy; or one-1 mg tablet twice daily, given as one tablet one hour before chemotherapy and one tablet 12 hours later Prevention of CINV: Injection: 10 mcg/kg IV within 30 min before the initiation of chemotherapy and only on the days chemotherapy is given Prevention of n/v with moderately emetogenic chemotherapy and/or highly emetogenic chemotherapy regimens of up to five consecutive days duration: Transdermal patch: apply one patch to the upper outer arm a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion Prevention of n/v with moderately emetogenic chemotherapy and/or anthracycline and cyclophosphamide combination chemotherapy regimens: Extended-release injection: 10 mg subcutaneous injection at least 30 minutes before the start of emetogenic chemotherapy on Day 1; do not administer more frequently than once every 7 days. Radiation (TBI or fractionated abdominal radiation): Tablet: two 1 mg tablets once daily within one hour of radiation Prevention of PONV: Injection: 1 mg IV before induction of anesthesia or immediately before reversal of anesthesia Treatment of PONV: Injection: 1 mg IV	Prevention of CINV: Injection: 10 mcg/kg IV	Extended-release subcutaneous injection: Intended for administration by a healthcare provider by a slow, sustained injection over 20 to 30 seconds; administer in skin of the back of the upper arm or in the skin of the abdomen at least 1 inch away from the umbilicus; do not substitute non-kit components for any of the components from the kit for administration. Transdermal patch: The patch may be worn for up to seven days depending on the duration of the chemotherapy regimen.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
Ondansetron	Injection: 2 mg/mL vials (single- and multi-use vials) ODT: 4 mg 8 mg Oral soluble film: 4 mg 8 mg Oral solution: 4 mg/5 mL Tablet: 4 mg 8 mg 16 mg 24 mg	<u>Prevention of n/v associated with highly emetogenic cancer chemotherapy</u>: ODT, oral soluble film, oral solution, tablet: 24 mg given as three 8 mg tablets/films administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2 <u>Prevention of n/v associated with initial and repeat courses of emetogenic chemotherapy</u>: Injection: three 0.15 mg/kg doses IV up to a maximum of 16 mg per dose; the first dose is given over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given four and eight hours after the first dose <u>Prevention of n/v associated with moderately emetogenic cancer chemotherapy</u>: ODT, oral soluble film, oral solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) oral solution given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose eight hours later; then twice daily (every 12 hours) for one to two days after the completion of chemotherapy <u>Prevention of n/v associated With radiotherapy (TBI):</u> ODT, oral soluble film, oral solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) of oral solution given one to two hours before each fraction of radiotherapy administered each day <u>Prevention of n/v associated with radiotherapy (single high-dose fraction radiotherapy to the abdomen)</u>: ODT, oral soluble film, oral	<u>Prevention of n/v associated with initial and repeat courses of emetogenic chemotherapy</u>: Injection: three 0.15 mg/kg doses IV up to a maximum of 16 mg per dose; the first dose is given over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given four and eight hours after the first dose <u>Prevention of n/v associated with moderately emetogenic cancer chemotherapy</u>: ODT, oral soluble film, oral solution, tablet (patients ≥12 years of age): same dosing as adults ODT, oral soluble film, oral solution, tablet (patients four to 11 years of age): one 4 mg tablet, ODT, soluble film, or 5 mL (4 mg) of oral solution given three times daily with the first dose given 30 min before the start of emetogenic chemotherapy and subsequent doses four and eight hours later; then three times daily (every eight hours) for 1 to 2 days after completion of chemotherapy <u>Prevention of PONV:</u> Injection: a single 0.1 mg/kg dose for patients weighing ≤40 kg; or a single 4 mg dose for patients weighing >40 kg, administered over 2 to 5 min immediately prior to or following anesthesia induction, or	Oral soluble film: each soluble film should be allowed to completely dissolve before administering any subsequent film.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
		solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) of oral solution given one to two hours before radiotherapy, with subsequent doses every eight hours after the first dose for one to two days after completion of radiotherapy <u>Prevention of n/v associated with radiotherapy (daily fractionated radiotherapy to the abdomen)</u>: ODT, oral soluble film, oral solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) of oral solution given one to two hours before radiotherapy, with subsequent doses every eight hours after the first dose for each day radiotherapy is given <u>Prevention of PONV:</u> Injection: 4 mg (undiluted) IV over two to five minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within two hours after surgery; OR 4 mg (undiluted) IM as a single dose ODT, oral soluble film, oral solution, tablet: 16 mg given as two 8 mg tablets, ODT tablets, soluble films, or 20 mL (16 mg) of oral solution one hour before induction of anesthesia	postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring shortly after surgery	
Palonosetron	Injection: 0.25 mg/5 mL (single-use vial)	<u>Prevention of CINV:</u> Injection (adults): a single 0.25 mg IV dose given over 30 seconds, approximately 30 minutes before the start of chemotherapy <u>Prevention of PONV:</u> Injection: a single 0.075 mg IV dose given over 10 seconds immediately before the induction of anesthesia	Injection (pediatric): a single 20 mcg/kg (max 1.5 mg) IV dose given over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy	Not applicable

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
Substance P/NK_1 Receptor Antagonists				
Aprepitant	Capsule: 40 mg 80 mg 125 mg Combination pack (capsule): 80 and 125 mg Oral suspension: 125 mg/5 mL (after mixing)	<u>Prevention of CINV in adults and pediatric patients ≥ 12 years:</u> Capsule: 125 mg one hour prior to chemotherapy treatment on day one and 80 mg once daily on days two and three Oral suspension for adults who are unable to swallow capsules: 125 mg one hour prior to chemotherapy treatment on day one and 80 mg once daily on days two and three <u>Prevention of PONV:</u> Capsule: 40 mg within three hours prior to induction of anesthesia	<u>Prevention of CINV in pediatric patients 6 months to < 12 years:</u> Oral suspension: 3 mg/kg (maximum 125 mg) on day one, 2 mg/kg (maximum 80 mg) on days two and three	Aprepitant can be given with or without food Aprepitant is given as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist
Fosaprepitant	Injection: 150 mg/mL single-use vial	<u>Prevention of cancer CINV:</u> Highly Emetic Chemotherapy (HEC Single Dose Regimen): 150 mg administered on day one 30 minutes prior to chemotherapy Moderately Emetic Chemotherapy: 150 mg IV about 30 minutes before chemotherapy	Not applicable	Fosaprepitant is administered IV as a 20 to 30 minute infusion Fosaprepitant is given as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist
Rolapitant	Tablet: 90 mg	<u>Prevention of delayed CINV, including, but not limited to, highly emetogenic chemotherapy:</u> 180 mg given approximately 1 to 2 hours prior to chemotherapy on day 1	Not applicable	Rolapitant is given as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist
Combination product				
Palonosetron/ netupitant	Capsule: 300 mg netupitant/ 0.5 mg palonosetron	<u>Prevention of CINV, including, but not limited to, highly emetogenic chemotherapy:</u> One capsule given 1 hour prior to the start of chemotherapy	Not applicable	This combination product is part of a regimen that includes a corticosteroid
Miscellaneous				
DICLEGIS	Delayed-release tablet: 10 mg doxylamine succinate/ 10	Take two tablets by mouth daily at bedtime. If symptoms are not adequately controlled, the dose can be increased to a maximum recommended dose	Not applicable	Should be taken on an empty stomach with a glass of water

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
	mg pyridoxine HCl	of four tablets daily (one in the morning, one mid-afternoon, and two at bedtime)		Swallow tablets whole (do not crush, chew, or split)
BONJESTA	Extended-release tablet: 20 mg doxylamine succinate/ 20 mg pyridoxine HCl	On day one, take one tablet at bedtime. On day two, if symptoms are not adequately controlled, the dose can be increased to one tablet in the morning and one tablet at bedtime. The maximum dose is two tablets daily, one in the morning and one at bedtime	Not applicable	Should be taken on an empty stomach with a glass of water Swallow tablets whole (do not crush, chew, or split)

Abbrv: CINV=chemotherapy-induced nausea and vomiting, IM=intramuscular, IV=intravenous, ODT=orally disintegrating tablet, PONV=postoperative nausea and vomiting, TBI=total body irradiation
*Supplied by multiple generic manufacturers in single-use and multi-use vial sizes.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
5-HT$_3$ Receptor Antagonists					
Dolasetron	No dose adjustment required.	No dose adjustment required in children. Approved for use in children two to 16 years (based on pharmacokinetic data in adults). Not studied in patients <2 years.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Granisetron	No dose adjustment required.	No dose adjustment required. Injection approved for CINV in children two to 16 years. Granisetron injection not studied in patients <2 years. Extended-release injection, ODT, tablet, transdermal patch: not studied in pediatrics.	Renal dose adjustment not required. Extended-release injection: avoid in patients with severe renal impairment (CrCl < 30mL/min); for patients with moderate renal impairment (30 to 59	Hepatic dose adjustment not required.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution. Extended-release injection: no available data on the use in pregnant women.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			mL/min), administer not more frequently than once every 14 days.		
Ondansetron	No dose adjustment required.	Injection (6 months to 18 years for prevention of CINV): weight-based dosing up to 16 mg per dose three times daily. Injection (one month to 12 years for prevention of PONV): single 0.1 mg/kg for patients ≤40 kg or a single 4 mg dose for patients >40 kg. Injection: not studied in patients <1 month of age. ODT, oral solution, oral soluble film, tablet (≥12 years): no dose adjustment required. ODT, oral solution, oral soluble film, tablet (four to 11 years for moderately emetogenic CINV): half the adult dose. ODT, oral solution, oral soluble film, tablet: not studied in patients <4 years or in the prevention of CINV due to highly emetogenic chemotherapy, PONV, or RINV.	Renal dose adjustment not required.	In severe hepatic impairment (Child-Pugh score ≥10), do not exceed a single 8 mg dose on the first day of chemotherapy or a total daily dose of 8 mg. There is no experience beyond first-day administration in these patients.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Palonosetron	No dose adjustment required.	Injection (1 month to <17 years for prevention of CINV): a single weight-based dose (max 1.5 mg) before the start of chemotherapy	Renal dose adjustment not required.	Hepatic dose adjustment not required.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Substance P/NK$_1$ Receptor Antagonists					
Aprepitant	Use caution when	Oral suspension (6 months to <12 years for	Renal dose adjustment	Use with caution in	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	dosing elderly patients.	prevention of CINV): a single weight-based dose on days 1, 2, and 3 given 1 hour before chemotherapy	not required.	patients with severe hepatic impairment (Child-Pugh score >9).	Unknown whether excreted in breast milk; use with caution.
Fosaprepitant	Use caution when dosing elderly patients.	Safety and efficacy in children have not been established.	Renal dose adjustment not required.	Use with caution in patients with severe hepatic impairment (Child-Pugh score >9).	Unclassified† Unknown whether excreted in breast milk; use with caution.
Rolapitant	No dose adjustment required.	Safety and efficacy in children have not been established.	Renal dose adjustment required.	Avoid use in patients with severe hepatic impairment (Child-Pugh class C).	Unclassified† Unknown whether excreted in breast milk; use with caution
Combination product					
Palonosetron/ netupitant)	Use caution when dosing elderly patients.	Safety and efficacy in children have not been established.	No dose adjustment is needed for mild to moderate renal impairment; avoid use in severe impairment.	No dose adjustment is needed for mild to moderate hepatic impairment (Child-Pugh score 5 to 8); avoid use in severe impairment.	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
Miscellaneous					
Doxylamine succinate/ pyridoxine HCl	Not studied in the elderly population	Safety and efficacy in children have not been established.	Not studied in renal dysfunction	Not studied in hepatic dysfunction	Pregnancy Category A (DICLEGIS) Unclassified† (BONJESTA) Women should not breastfeed while using doxylamine succinate/ pydridoxine HCl

Abbrv: CINV=chemotherapy-induced nausea and vomiting, ODT=orally disintegrating tablet, PONV=postoperative nausea and vomiting, RINV=radiation-induced nausea and vomiting

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

*****Pregnancy Category B=No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery.
- Treatment of CINV or RINV generally involves the use of multiple agents that affect different receptor types, such as 5-HT_3 receptor antagonists, substance P/NK_1 receptor antagonists, and corticosteroids (AGA, 2001; Herrstedt et al, 2016; Hesketh et al, 2016; Roila et al, 2010).
- Choice of agents generally depends upon the relative emetogenic potential of the chemotherapy regimen (AGA, 2001; Hesketh et al, 2016; Roila et al, 2010).
- The 5-HT_3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV (AGA, 2001; Gupta et al, 2016; Herrstedt et al, 2016; Hesketh et al, 2016; Gan et al, 2014; Roila et al, 2010).
- ALOXI (palonosetron) has a longer half-life than the other 5-HT_3 receptor antagonists, and single-dose therapy with ALOXI (palonosetron) is reported to be more effective than other medications in the class, particularly at preventing delayed emesis (Aapro et al, 2005; Billio et al, 2010; Botrel et al, 2011; Dong et al, 2011; Eisenberg et al, 2003; Gralla et al, 2003; Kaushal et al, 2010; Kovacs et al, 2016; Likun et al, 2011; Simino et al, 2016; Suzuki et al, 2016).
- In addition to CINV, granisetron and ZOFRAN (ondansetron) are also indicated for the treatment of RINV and have been shown to be equally effective (Billio et al, 2010; Dabbous et al, 2010; Erhan et al, 2008; Jain et al, 2009; Spitzer et al, 2000).
- Treatment with EMEND (aprepitant) has been shown to be effective for the prevention of CINV in combination with various 5-HT_3 receptor antagonists and dexamethasone (Hesketh et al, 2016; Herrington et al, 2008; Grunberg et al, 2011; Rapoport et al, 2010; Yeo et al, 2009; Herrstedt et al, 2005; Warr et al, 2005; Gralla et al, 2005).
- The fixed-dose combination AKYNZEO (palonosetron and netupitant) + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following moderately emetogenic chemotherapy (Aapro et al, 2014); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (Gralla et al, 2014).
- The addition of EMEND (aprepitant) to a 5-HT_3 receptor antagonist and dexamethasone regimen resulted in a greater proportion of patients achieving complete response (Gralla et al, 2005; De Wit et al, 2004; Poli-Bigelli et al, 2003; Hesketh et al, 2003; Martin et al, 2003).
- A 2016 meta-analysis found that when compared to other 5-HT3 antagonists and NK_1 antagonists, EMEND (aprepitant) reduces incidence of PONV, and need for rescue medications (Singh et al, 2016).
- DICLEGIS and BONJESTA are fixed dose combination drug products of doxylamine succinate and pyridoxine HCl , and both are indicated for the treatment of NVP in women who do not respond to conservative management. The combination of these agents was previous available in the United States under the name brand BENDECTIN®.
- The 2016 ASCO antiemetic guidelines recommend a three-drug combination of a NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone as first-line therapy for the prevention of CINV due to highly emetogenic chemotherapy agents. For moderately emetogenic agents, a two-drug combination of ALOXI (palonosetron) plus dexamethasone is recommended (Hesketh et al, 2016).
- A 2016 expert opinion statement from ASER states that during the perioperative period, all patients should receive PONV prophylaxis (Gupta et al, 2016).
- The clinical consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first line pharmacologic therapy (ACOG, 2015).
- EMEND (aprepitant) has been considered superior to a 5-HT_3 receptor antagonist in the prevention of delayed emesis induced by moderately emetogenic chemotherapy in breast cancer patients receiving a combination of anthracycline and cyclophosphamide treated with aprepitant, a 5-HT_3 antagonist, and dexamethasone; therefore, EMEND (aprepitant) should be used to prevent delayed n/v (Roila et al, 2010).
- The 5-HT_3 receptor antagonists are generally very well tolerated. There is a warning and general precaution for ANZEMET (dolasetron) regarding the risk of arrhythmias. ZOFRAN (ondansetron) and granisetron have QTc prolongation as a general precaution, but the incidence of ECG changes has been less than 1%. In addition, the development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists.
- Granisetron and ZOFRAN (ondansetron) are the only 5-HT_3 receptor antagonists that are available generically.
- All of the 5-HT_3 receptor antagonists are available as injections and all but ALOXI (palonosetron) are currently available as oral products. Granisetron is also available in a transdermal patch (SANCUSO) and extended-release injection (SUSTOL).

Table 4. Advantages and Disadvantages of Antiemetics – 5-HT$_3$ Receptor Antagonists

Drug	Advantages	Disadvantages
5-HT$_3$ Receptor Antagonists		
Dolasetron	• Approved for use in children ages two to 16 years of age. • Dolasetron injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients. • Pregnancy category B. • FDA indication for PONV.	• Not available generically. • Adverse effects of QTc prolongation.
Granisetron	• Injection products approved for use in children two to 16 years of age. • Available in different formulations including injection, tablets, and transdermal patch. • Oral tablets and injection are available generically. • Pregnancy category B. • SANCUSO patch has a long duration of effect, allowing for extended coverage of n/v as well as n/v that prevents the administration of oral therapies. • FDA indication for RINV (tablet) and prevention of PONV (injection).	• SANCUSO patch and SUSTOL extended-release injection are not available generically.
Ondansetron	• Safety and efficacy in pediatrics as young as 6 months. • Available in different formulations including injection, tablets, oral soluble film, and oral solution. • Available generically in injection, oral solution, and oral tablet formulations. • Pregnancy category B. • Oral formulations have FDA indication for RINV and PONV.	• ZUPLENZ not available generically. • Adverse effects of QTc prolongation.
Palonosetron	• Safety and efficacy in children ages 1 month to <17 years for prevention of CINV. • Pregnancy category B. • FDA indication for PONV. • Longest half-life (40 hours) of the 5-HT$_3$ receptor antagonists.	• Not available generically. • Only available as an injection.
Substance P/NK$_1$ Receptor Antagonists		
Aprepitant, fosaprepitant	• Available in different formulations including injection, capsules, and oral suspension. • Aprepitant capsules are available generically. • FDA indication for prevention of PONV (capsule).	• Aprepitant oral suspension and fosaprepitant are not available generically.
Rolapitant	• None	• Only approved for delayed CINV. • Only available as a tablet. • Not available generically. • Safety and effectiveness have not been established in children <18 years of age.
Combination Product		
Palonosetron/ netupitant	• Only available oral product containing a 5-HT$_3$ receptor antagonist and substance P/NK$_1$ receptor antagonist.	• Not available generically. • Safety and effectiveness have not been established in children <18 years of age. • Pregnancy Category C. • Only available as a capsule.

Drug	Advantages	Disadvantages
Miscellaneous		
Doxylamine succinate/pyridoxine HCl	• Only FDA-approved agent for the treatment of nausea and vomiting of pregnancy. • Initial dosing allows for once daily dosing.	• Available as individual components. • Only available as a tablet.

Abbrv: CINV=chemotherapy-induced nausea and vomiting, FDA=Food and Drug Administration, PONV=postoperative nausea and vomiting, RINV=radiation-induced nausea and vomiting

(Clinical Pharmacology, 2017; Micromedex, 2017)

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