Therapeutic Class Overview
Antiemetics (5-HT_3 Receptor Antagonists and Combinations)

Overview/Summary:
The Type 3 serotonin (5-HT_3) receptor antagonists and combination products are Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and/or radiation-induced nausea and vomiting (RINV).[1-10] A These agents work via blockade of the 5-HT_3 receptors both peripherally on vagal nerve terminals, and centrally in the chemoreceptor trigger zone of the area postrema. By blocking these receptors, these agents disrupt the signal to vomit and reduce the sensation of nausea.[1-10] Netupitant, a substance P/neurokinin-1 (NK_1) receptor antagonist is formulated with palonosetron (Akynzeo®) and is indicated for CINV.[10] Netupitant works via blockade of tachykinin family NK_1 receptors broadly distributed in the central and peripheral nevous systems, thus preventing substance P from activating the receptors. Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.[10] Although the medications in this class vary slightly in their FDA-approved indications, expert guidelines do not generally differentiate between them and consider them equally effective. The one exception is in regard to moderately-emetogenic antineoplastic-induced nausea and vomiting, where consensus guidelines recommend palonosetron (for one day only) as the first line agent over other 5-HT_3 antagonists.[11-13] The Pediatric Oncology Group of Ontario recommends either ondansetron or granisetron as first line agents for pediatric patients for the prevention of antineoplastic-induced nausea and vomiting.[14] Clinical trials are summarized in Table 10 and also include recommendations for use in postoperative nausea and vomiting prophylaxis and pregnancy induced nausea and vomiting.[11-17]

The single entity 5-HT_3 agents are generally formulated as a tablet or solution for injection and include dolasetron (Anzemet®), granisetron, ondansetron (Zofran®) and palonosetron (Aloxi®). Other formulations include granisetron transdermal patch (Sancuso®) and ondansetron orally disintegrating tablet (Zofran ODT®) and oral solution.[5-7] Zuplenz®, an oral soluble film formulation of ondansetron is placed in the mouth where it dissolves within four to twenty seconds and is then swallowed with the saliva with or without liquid.[8] In addition, netupitant is formulated with palonosetron (Akynzeo®) as an oral capsule.[10] In general, there are some differences in regards to duration of action, metabolic pathways, routes of administration and dosing schedules of these agents. Palonosetron is considered a second generation 5-HT_3 antagonist and has a 30- to 100-fold higher affinity for the 5-HT_3 receptor and a significantly longer half-life than the other first-generation agents.[18] Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically.

Table 1. Current Medications Available in Therapeutic Class[1-7]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Dolasetron (Anzemet®)	Chemotherapy-induced nausea and vomiting prophylaxis (tablet)*; Postoperative nausea and vomiting prophylaxis and treatment (injection)	Tablet: 50 mg 100 mg Solution for IV injection, vial: 12.5 mg/0.625 mL 100 mg/5 mL 500 mg/25 mL	-
Granisetron†† (Sancuso®)	Chemotherapy-induced nausea and vomiting prophylaxis †; Radiation-induced nausea and vomiting prophylaxis (tablet)‡	Solution for injection, vial: 1 mg/1 mL 4 mg/4 mL 0.1 mg/1 mL	a

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours	
Ondansetron (Zofran®††, Zofran ODT®††, Zuplenz®)	Chemotherapy-induced nausea and vomiting prophylaxis §; Radiation-induced nausea and vomiting prophylaxis (oral formulations) ‖; Postoperative nausea and vomiting prophylaxis; Postoperative nausea and vomiting treatment (injection)	ODT: 4 mg 8 mg Oral Film: 4 mg 8 mg Oral Solution: 4 mg/5 mL Solution for injection, vial: 4 mg/2 mL 40 mg/20 mL Tablet: 4 mg 8 mg 24 mg	a
Palonosetron (Aloxi®)	Chemotherapy-induced nausea and vomiting prophylaxis	Solution for IV injection, vial: 0.25 mg/5 mL 0.075mg/1.5 mL	-
Combination Product			
Netupitant/ palonosetron (Akynzeo®)	Chemotherapy-induced nausea and vomiting prophylaxis**	Capsule: 300/0.5 mg	-

* Moderately emetogenic cancer chemotherapy, including initial and repeat courses.
† Tablet/injection: Initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. Patch: moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.
‡ Including total body irradiation and fractionated abdominal radiation.
§ Injection: initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Oral agents: Initial and repeat courses of moderately emetogenic cancer chemotherapy and highly emetogenic cancer chemotherapy, including cisplatin
‖ Including total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen
¶ Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy
# For up to 24 hours following surgery.
** Acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
†† Generic available in at least one dosage form or strength

Evidence-based Medicine

- The FDA approval of transdermal granisetron was based on the results of an unpublished randomized, double-blind clinical trial that evaluated 641 patients receiving moderately or highly emetogenic chemotherapy. The transdermal formulation demonstrated noninferiority to the standard dose of oral granisetron in achieving complete control of chemotherapy-induced nausea and vomiting.[19]

- The approval of netupitant/palonosetron was based on the efficacy and safety in preventing CINV in patients receiving moderately emetogenic chemotherapy (MEC), anthracycline plus cyclophosphamide (A/C) chemotherapy or highly emetogenic chemotherapy (HEC) in three clinical trials. All of these trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone.[20,21]
- Numerous clinical trials have compared the agents in this class to other medications in the same class, other medications with the same indications, and placebo. In general most studies used adult patients, with a few clinical trials evaluating the use of these agents in children. The results of these trials have varied slightly in efficacy of a particular agent but overall no particular agent was found to be consistently more efficacious than another agent.[22-52]
    - Several clinical studies were evaluated in a meta-analysis and have shown that palonosetron is more effective than the first-generation agents in the prevention of acute CINV (P=0.0003), delayed CINV (P<0.00001), and overall phase of CINV (P<0.00001) when used to prevent nausea and vomiting associated with moderately emetogenic chemotherapy.[34]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Expert guidelines do not generally differentiate between the 5-HT_3 antagonists and consider them equally effective.[11-13]
        - When trying to prevent moderately-emetogenic antineoplastic-induced nausea and vomiting, consensus guidelines recommend palonosetron (for one day only) as the first line agent over other 5-HT_3 antagonists
    - The Pediatric Oncology Group of Ontario recommends either ondansetron or granisetron as first line agents for pediatric patients for the prevention of antineoplastic-induced nausea and vomiting.[14]

- Other Key Facts:
    - In terms of pharmacokinetics, palonosetron has a longer half-life that the other 5-HT_3 receptor antagonists.[9]
    - The most common side effects of the 5-HT_3 receptor antagonists are constipation, headache, and asthenia, and the side effect profiles appear comparable.[1-10]
    - Safety and efficacy of granisetron patch and netupitant/palonosetron in children have not been established, while the other 5-HT_3 receptor antagonists are approved for the use in children in certain indications.[1-10]
    - Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically.
    - All of the single entity 5-HT_3 receptor antagonists are available by injection and all but palonosetron are currently available by the oral route. Granisetron is formulated as a transdermal patch.[1-10]

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Therapeutic Class Review
Antiemetics (5-HT_3 Receptor Antagonists and Combinations)

Overview/Summary

The Type 3 serotonin (5-HT_3) receptor antagonists and combination products are Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and/or radiation-induced nausea and vomiting (RINV).[1-10] These agents work via blockade of the 5-HT_3 receptors both peripherally on vagal nerve terminals, and centrally in the chemoreceptor trigger zone of the area postrema. By blocking these receptors, these agents disrupt the signal to vomit and reduce the sensation of nausea.[1-10] Netupitant, a substance P/neurokinin-1 (NK_1) receptor antagonist is formulated with palonosetron (Akynzeo®) and is indicated for CINV.[10] Netupitant works via blockade of tachykinin family NK_1 receptors broadly distributed in the central and peripheral nevous systems, thus preventing substance P from activating the receptors. Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.[10] Although the medications in this class vary slightly in their FDA-approved indications, expert guidelines do not generally differentiate between them and consider them equally effective. The one exception is in regard to moderately-emetogenic antineoplastic-induced nausea and vomiting, where consensus guidelines recommend palonosetron (for one day only) as the first line agent over other 5-HT_3 antagonists.[11-13] The Pediatric Oncology Group of Ontario recommends either ondansetron or granisetron as first line agents for pediatric patients for the prevention of antineoplastic-induced nausea and vomiting.[14] Clinical guidelines are summarized in Table 10 and also include recommendations for use in postoperative nausea and vomiting prophylaxis and pregnancy induced nausea and vomiting.[11-17]

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Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Dolasetron (Anzemet®)	5-HT_3 receptor antagonist	-
Granisetron* (Sancuso®)	5-HT_3 receptor antagonist	a
Ondansetron (Zofran®*, Zofran ODT®*, Zuplenz®)	5-HT_3 receptor antagonist	a
Palonosetron (Aloxi®)	5-HT_3 receptor antagonist	-
Combination Product		
Netupitant/palonosetron (Akynzeo®)	substance P and NK_1 receptor antagonist/5-HT_3 receptor antagonist	-

*Generic available in at least one dosage form or strength

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[1-10]

Generic Name	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis	Radiation-Induced Nausea and Vomiting (RINV) prophylaxis	Postoperative Nausea and Vomiting (PONV)	
			Prophylaxis	Treatment
Single Entity Products				
Dolasetron	a (tab*)		a (inj)	a (inj)
Granisetron	a †	a (tab‡)		
Ondansetron	a §	a (oral‖)	a	a (inj)
Palonosetron	a		a #	
Combination Product				
Netupitant/ palonosetron	a **			

* Moderately emetogenic cancer chemotherapy, including initial and repeat courses.
† Tablet/injection: Initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. Patch: moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.
‡ Including total body irradiation and fractionated abdominal radiation.
§ Injection: initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Oral agents: Initial and repeat courses of moderately emetogenic cancer chemotherapy and highly emetogenic cancer chemotherapy, including cisplatin
‖ Including total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen
¶ Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy
# For up to 24 hours following surgery.
** Acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

Pharmacokinetics

Table 3. Pharmacokinetics[1,27-37]

Generic Name	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products				
Dolasetron, injection	No data	53 (Hydro-dolasetron)	Yes; Hydro-dolasetron	Dolasetron:<10 minutes
Dolasetron, oral				Hydrodolasetron: 7.3
Granisetron, injection	>24	12	None	9
Granisetron, oral				
Granisetron, patch	Up to 7 days			Not reported
Ondansetron, injection	9	5	None	3.0-5.5
Ondansetron, oral				
Palonosetron, injection	>24	40	None	40
Combination Product				
Netupitant/ palonosetron, oral	>24/>24	<1/40	None	96/44

Clinical Trials

The FDA approval of transdermal granisetron was based on the results of an unpublished randomized, double-blind clinical trial that evaluated 641 patients receiving moderately or highly emetogenic chemotherapy. The transdermal formulation demonstrated noninferiority to the standard dose of oral granisetron in achieving complete control of chemotherapy-induced nausea and vomiting.[19]

The approval of netupitant/palonosetron was based on the efficacy and safety in preventing CINV in patients receiving moderately emetogenic chemotherapy (MEC), anthracycline plus cyclophosphamide (A/C) chemotherapy or highly emetogenic chemotherapy (HEC) in three clinical trials. All of these trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone.[20,21]

In trial one, NEPA 07-07, 694 chemotherapy naïve individuals ≥ 18 years of age who were scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents. Significantly more patients receiving netupitant/palonosetron compared to palonosetron alone had a complete response (CR), defined as no emesis and no rescue medication use, during the overall phase (P=0.018, P=0.017 P=0.004 for 100, 200 and 300 mg netupitant respectively; P=0.027 for aprepitant plus ondansetron; no P value reported for palonosetron alone).[20] In trial two, NEPA 08-18, 1,455 chemotherapy naïve individuals ≥18 years of age who were scheduled to receive an anthracycline/ cyclophosphamide (A/C) regimen on Day 1 for treatment. A CR during the delayed phase was found to be significantly greater in the netupitant/palonosetron group as compared to the palonosetron group (76.9% vs 69.5%; P=0.001). During the acute phase and the overall phase, more patients receiving netupitant/palonosetron vs palonosetron experienced a CR (acute, P=0.047; overall, P=0.001).[20] The final trial, NEPA 10-29, included 413 individuals ≥18 years of age who were chemotherapy naïve and scheduled to receive repeated consecutive courses of chemotherapy with either HEC or MEC for treatment of a malignant tumor. The majority of adverse events were mild to moderate in intensity. The most common treatment-emergent, drug-related adverse events were constipation (netupitant/palonosetron, 3.6%; palonosetron/aprepitant, 1.0%) and headache (netupitant/palonosetron and palonosetron/aprepitant were both 1.0%). Adverse event rates did not increase over multiple cycles.[21]

Numerous clinical trials have compared the agents in this class to other medications in the same class, other medications with the same indications, and placebo. In general most studies used adult patients, with a few clinical trials evaluating the use of these agents in children. The results of these trials have varied slightly in efficacy of a particular agent but overall no particular agent was found to be consistently more efficacious than another agent.[22-52] There is one exception in regard to moderately-emetogenic antineoplastic-induced nausea and vomiting. Several clinical studies were evaluated in a meta-analysis and have shown that palonosetron is more effective than the first-generation agents in the prevention of acute CINV (P=0.0003), delayed CINV (P<0.00001), and overall phase of CINV (P<0.00001). Subgroup analyses showed statistically significant differences in favor of both 0.25 mg and 0.75 mg of palonosetron in prevention of all phases of CINV. There were no statistically significant differences between 0.25 and 0.75 mg of palonosetron. Compared with the first-generation 5-HT$_3$ antagonists, 0.75 mg of palonosetron showed a statistically significant difference in the occurrence of constipation (P=0.04).[34]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting				
Grunberg et al[19] Granisetron transdermal system applied 24 to 48 hr before first dose of chemotherapy and left in place for days days vs granisetron 2 mg orally once daily one hour before each dose of chemotherapy	DB, MC, PG, RCT Patients 16 to 86 years of age, receiving moderately or highly emetogenic multi-day chemotherapy for histologically and/or cytologically confirmed cancer (ECOG status ≤2); life expectancy ≥3 month	N=641 7 days	Primary: Complete control of chemotherapy-induced nausea and vomiting from the first administration until 24 hours after the last administration of three to five days of moderately or highly emetogenic chemotherapy Secondary: Complete response, frequency of nausea, frequency of vomiting, time to first episode of nausea or vomiting	Primary: Non-inferiority of granisetron transdermal patch was confirmed, with 60.2% of patients in the granisetron transdermal patch arm and 64.8% in the oral granisetron arm achieving complete control (difference, -5.51%; 95% CI, -13.6% to 2.5%). No significant differences (P>0.05) were found between the treatment groups following secondary analysis by pre-defined strata (gender, chemotherapy type, history, duration and emetogenicity), although patients receiving highly emetogenic therapy were more likely to vomit (complete control 57%) than patients receiving moderately emetogenic therapy (complete control 77%). Secondary: No significant differences between treatments were detected. Adherence in the granisetron transdermal patch was >75% in 90% of the group. Toxicities in both arms were generally minor, with constipation and headache most common. No significant application site irritation occurred.
Aapro et al[20] NEPA 08-18 Netupitant/palonosetron (300 mg/0.5 mg) plus dexamethasone 12 mg for one dose	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve with an ECOG	N=1455 One cycle	Primary: Complete response (no emetic episode and no rescue medication) in preventing	Primary: Complete response during the delayed phase was seen in 76.9% of the netupitant/palonosetron group compared to 69.5% of the palonosetron group (P=0.001). Secondary: Complete response during the acute phase was seen in 88.4% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs palonosetron 0.5 mg plus dexamethasone 20 mg for one dose	performance status of 0,1 or 2 and scheduled to receive an anthracycline/ cyclophosphamide regimen on Day 1 for treatment of a solid malignant tumor		nausea and vomiting during the delayed phase Secondary: Complete response during the acute phase, the overall phase; Complete protection during the acute, delayed and overall phases; no emesis during the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases; proportion of patients with scores reflecting "no impact on daily life on daily life using the FLIE questionnaire	the netupitant/palonosetron group compared to 85.0% of the palonosetron group (P=0.047). Complete response during the overall phase was seen in 74.3% of the netupitant/palonosetron group compared to 66.6% of the palonosetron group (P=0.001). Significantly more patients in the netupitant/palonosetron group reported no emesis during the acute, delayed and overall phases compared with the palonosetron group (P=0.025, P=0.004 and P<0.001, respectively). Significantly more patients in the netupitant/palonosetron group reported no significant nausea during the delayed and overall phases, but not the acute phase, compared with the palonosetron group (delayed, P=0.014; overall, P=0.020; acute, P=0.747). Complete protection was achieved by more patients who received netupitant/palonosetron compared to palonosetron during the delayed (67.3% vs 60.3%; P=0.005) and overall phases (63.8% vs 57.9%; P=0.020). FLIE questionnaire results showed that a greater proportion of patients receiving netupitant/palonosetron versus patients receiving palonosetron reported no impact on daily living from CINV (nausea domain, P=0.015; vomiting domain, P=0.001; combined domain, P=0.005).
Hesketh et al[20] NEPA 07-07	DB, DD, PG, MC, RCT	N=694 One cycle	Primary: CR during the overall phase	Primary: During the overall phase, 87.4% of patients in the netupitant/palonosetron 100 mg/0.5 mg group achieved CR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Netupitant/palonosetron 100 mg/0.5 mg for one dose vs netupitant/palonosetron (200 mg/0.5 mg) for one dose vs netupitant/palonosetron (300 mg/0.5 mg) for one dose vs palonosetron 0.5 mg for one dose vs aprepitant 125 mg plus ondansetron 32 mg IV (exploratory arm) for one dose (All groups received dexamethasone therapy-varying doses based on study drug assigned)	Patients ≥18 years of age with histologically or cytologically confirmed malignant disease featuring solid tumor(s), chemotherapy naïve, Karnofsky index ≥ 70%; scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents		period Secondary: CR during the acute and delayed phases; CP during the acute, delayed, and overall phases; no emesis during the acute, delayed, and overall phases; no significant nausea during the acute, delayed, and overall phases	(P=0.018); 87.6% in the netupitant/palonosetron 200 mg/0.5 mg group (P=0.017); 89.6%; in the netupitant/palonosetron 300 mg/0.5 mg group (P=0.004); 76.5% in the palonosetron alone group (no P value reported) and 86.6% in the aprepitant plus ondansetron group (P=0.027). Secondary: Complete response during the acute phase was seen in 98.5% of patients in the netupitant 300 mg/palonosetron 0.5mg group compared to 89.7% in the palonosetron alone group (P≤0.01). Complete response during the delayed phase was seen in 90.4% of patients in the netupitant 100 mg/palonosetron 0.5 mg group (P≤0.05), 91.2% in the netupitant 200 mg/palonosetron 0.5 mg group (P≤0.01) and 90.4 % of the netupitant 300 mg/palonosetron 0.5 mg group (P≤0.05) compared to 80.1% in the palonosetron group (no P value reported) and 88.8% in the aprepitant plus ondansetron group (P≤0.05). Complete protection was reported by more individuals in the netupitant/palonosetron 300 mg/0.5 mg group compared to palonosetron alone in the acute, delayed and overall phases (P≤0.01, P≤0.05 and P≤0.01, respectively). Significantly more patients in the netupitant/palonosetron 300 mg/0.5 mg group reported no emesis during the acute, delayed and overall phases compared to the palonosetron alone group (all P values ≤0.01). For the endpoint of no significant nausea, the netupitant/ palonosetron 300 mg/0.5 mg group reported higher rates of 98.5% (P≤0.05) for the acute phase, 90.4% (P≤0.01) for the delayed phase and 89.6% (P≤0.05) for overall phase compared to palonosetron alone (93.4%, 80.9% and 79.4%, respectively; no P values reported). The exploratory arm of aprepitant plus

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ondansetron reported rates 94.0% for acute phase, 88.1% for delayed phase, and 85.8% for overall phase (no P values reported).
Gralla et al[21] NEPA 10-29 Netupitant/palonosetron (300 mg/0.5 mg) plus dexamethasone for one dose (dose based on the emetogenic potential of the chemotherapy regimen) vs palonosetron 0.5 mg on Day 1 plus aprepitant (125 mg Day 1 and 80 mg Days 2 to 3) plus dexamethasone (dose based on the emetogenic potential of the chemotherapy regimen)	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve with an ECOG performance status of 0 to 2 and scheduled to receive repeated consecutive courses of chemotherapy with either highly or moderately emetogenic agents for treatment of a malignant tumor	N=413 One cycle	Primary: Safety (AEs, vital sign measurements, laboratory tests including CTnI, physical examination ECG recordings including LVEF) Secondary: CR during the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases	Primary: The most common treatment-emergent, drug-related AEs reported in the treatment groups were constipation (netupitant/palonosetron, 3.6%; palonosetron/aprepitant, 1.0%) and headache (netupitant/palonosetron and palonosetron/aprepitant, both 1.0%). AEs did not increase over multiple cycles, and the incidence, type and frequency of treatment-emergent AEs was similar for both groups throughout the study. The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities. Secondary: CR rates during the overall phase were high in both treatment groups over all six cycles of chemotherapy, ranging from 81% to 92% in the netupitant/palonosetron group and from 76% to 88% in the palonosetron/aprepitant group. CR rates were numerically greater for patients receiving netupitant/palonosetron during the overall phase and the delayed phase. CR rates were similar for the treatment groups during the acute phase (no P values reported).
Eisenberg et al[22] Dolasetron 100 mg IV vs palonosetron 0.25 mg IV vs	DB, MC, PG, RCT Patients receiving moderately emetogenic chemotherapy, study drug given 30 minutes before chemotherapy, dexamethasone	N=592 5 days	Primary: Complete response (no emetic episodes and no need for rescue medication) during the first 24 hours after chemotherapy	Primary: The proportion of patients with complete response was not statistically different between the two palonosetron doses and dolasetron (palonosetron 0.25 mg 63% vs dolasetron 100 mg 52.9% [97.5% CI, -1.7% to 21.9%; *P*=0.049]), (palonosetron 0.75 mg 57.1% vs dolasetron 100 mg 52.9% (97.5% CI, -7.7% to 16.2%; *P*=0.412)]. Note: Significance was *P*<0.025 using the one-sided Fisher exact test. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
palonosetron 0.75 mg IV	could be added 15 minutes before chemotherapy		Secondary: Complete response during hours 24-120	Complete response with palonosetron 0.75 mg and 0.25 mg were significantly higher in the delayed phase (hours 24-120) compared to dolasetron (palonosetron 0.75 mg vs dolasetron 100 mg; *P*<0.001 and palonosetron 0.25 mg vs dolasetron 100 mg; *P*=0.004). Adverse effects were mild and similar for all 3 groups.
Lofters et al[23] Dolasetron 2.4 mg/kg IV followed by dolasetron 200 mg PO (arm 1) vs dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 2) vs dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO and dolasetron 200 mg PO (arm 3) vs ondansetron 32 mg IV or 8 mg PO BID without dexamethasone followed by ondansetron 8 mg PO BID (arm 4)	DB, PG, RCT Patients receiving 7 days of moderately emetogenic chemotherapy	N=696 7 days	Primary: Control of nausea and vomiting in the first 24 hours, complete response was no episode of emesis Secondary: MNS based on a visual analog scale, rates of complete protection after 7 days of treatment	Primary: In the dolasetron arms, 57% had complete protection for the first 24 hours compared to the ondansetron arms which had 67% (*P*=0.013). Secondary: MNS was more pronounced on the dolasetron arm, but the difference did not reach statistical significance (*P*=0.051). MNS was significantly reduced with the addition of dexamethasone to either dolasetron or ondansetron (*P*=0.001). Complete protection rates over 7 days was not statistically different (*P*=0.459) between dolasetron (36%) and ondansetron (39%). The addition of dexamethasone to both dolasetron and ondansetron showed statistical improvement compared to no dexamethasone in protection from emesis over 7 days (*P*<0.001). Dizziness and vision abnormalities were more common in the ondansetron group compared to dolasetron (*P*<0.001). Diarrhea was more common in the dolasetron group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by ondansetron 8 mg PO BID and dexamethasone 8 mg PO (arm 5) vs ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 6)				
del Giglio et al[24] Granisetron various IV and PO regimens vs ondansetron various IV and PO regimens	MA, RCT CINV	14 studies which included 6,467 patients with >25 patients per arm Duration varied	Primary: Comparison of prophylaxis of acute or delayed nausea and vomiting in highly or moderately emetogenic chemotherapy Secondary: Not reported	Primary: For all scenario comparisons (acute highly emetogenic, acute moderately emetogenic, delayed highly emetogenic, delayed moderately emetogenic), there were no statistical differences in efficacy between granisetron and ondansetron for rates of nausea or vomiting (*P* value not given). There was only one study that showed differences in toxicity between granisetron and ondansetron. In this study, ondansetron was associated with more dizziness and abnormal vision than granisetron (*P* value not given). Secondary: Not reported
Jaing et al[25] Granisetron 0.5-1 mg PO	OL, PRO, RCT, XO Patients 3-18 years old	N=33 24 hours	Primary: Number of emetic episodes within 24 hours of	Primary: Complete efficacy for granisetron and ondansetron was 60.6% and 45.5%, respectively (*P*=0.227).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 0.15 mg/kg IV for 2 doses (1 hour prior to chemotherapy and 4 hours later) and then a single PO dose (8 hours after first dose)			chemotherapy (complete efficacy was defined as no emetic episodes and no need for rescue medication) Secondary: Therapeutic success (defined as 0-2 emetic episodes), therapeutic failure (defined as 3 or more vomiting episodes)	Secondary: Therapeutic success was 84.8% in the granisetron group and 87.9% in the ondansetron group (*P*=1.00). Therapeutic failure for granisetron and ondansetron was 15.2% and 12.1%, respectively (*P*=1.00).
Dempsey et al[26] Granisetron 10 µg/kg or 1 mg IV vs ondansetron 8 mg IV vs ondansetron 32 mg IV	RETRO Prophylactic efficacy in patients with breast cancer treated with cyclophosphamide	Data from 6 centers in the United States N=224 (n=68 for ondansetron 8 mg IV, n=76 for ondansetron 32 mg IV, n=80 for granisetron 10 µg/kg or 1 mg IV) 72 hours	Primary: Incidence of acute nausea or vomiting (occurring within 24 hours of completion of chemotherapy) Secondary: Incidence of delayed emesis (occurring 25-72 hours after chemotherapy),	Primary: Incidence of acute nausea was statistically greater with ondansetron 8 mg IV (50%) than ondansetron 32 mg IV (26%) or granisetron (25%; *P*<0.01 for both comparisons). Incidence of acute emesis was not different amongst the three groups (*P* value not given). Secondary: Incidence of delayed nausea was 6% for ondansetron 8 mg IV, 9% for ondansetron 32 mg, and 9% for granisetron, which were not statistically different for any group (*P* value not given). Incidence of delayed emesis was not different amongst the three groups (*P* value not given).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			total control of CINV with or without dexamethasone	Total control of CINV without dexamethasone was 35% for ondansetron 8 mg, 33% for ondansetron 32 mg and 69% for granisetron (*P*=0.05 for granisetron vs ondansetron 8 mg). With the addition of dexamethasone, total control of CINV was not significantly different amongst the three groups (*P* value not given).
Lacerda et al[27] Granisetron 3 mg IV vs ondansetron 16 mg IV vs ondansetron 24 mg IV vs tropisetron 5 mg IV*	DB, PG, RCT Patients undergoing autologous or allogenic stem cell transplantation received daily IV doses of 5-HT_3 receptor antagonist during days of chemotherapy	N=100 Duration not specified	Primary: Complete response (no episodes of nausea or vomiting) Secondary: Major response (one episode), minimal response (2-4 episodes) and failure (more than 4 episodes of nausea or vomiting)	Primary: When comparing rates of complete response, there was a significant difference in the ondansetron 24 mg group (62.5%) compared to the granisetron group (27.8%; *P*=0.015) and tropisetron (16.7%; *P*=0.003). Complete response for ondansetron 16 mg was 31.3% but statistical difference from ondansetron 24 mg was not reported. There were no statistical differences in complete response rates between ondansetron 16 mg (31.3%), granisetron and tropisetron (*P* value not given). Secondary: There was a trend in the major response of ondansetron 24 mg versus granisetron (*P*=0.064). A significant difference was not observed with ondansetron 16 mg. No statistically significant differences were found between ondansetron 16 mg, granisetron or tropisetron (*P* values not given).
Walsh et al[28] Granisetron 10 µg/kg IV daily vs ondansetron 0.15 mg/kg IV every 8 hours	DB, PG, PRO, RCT Patients undergoing nontotal body irradiation-containing conditioning agents in hematopoietic	N=96 24 hours after completion of chemotherapy	Primary: Number of emetic episodes, nausea report until 24 hours after cessation of chemotherapy	Primary: The median number of emetic episodes for the granisetron arm was 3 and for the ondansetron arm was 1 (*P*=0.228). Rating of nausea was equal between the groups on all days of measurement (*P*=0.563 to *P*=1.0). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	stem cell transplant, in addition to dexamethasone and lorazepam		Secondary: Rates of complete response or major response	On day 1, complete response for the granisetron group was 83% and major response was 13%. Complete response for the ondansetron group was 90% and major response was 6%. These differences were not statistically significant (*P*=1.00). There were no differences in adverse effects.
Orchard et al[29] Granisetron 7.5 µg/kg/dose (≥18 years) or 10 µg/kg/dose (<18 years) every 12 hours vs ondansetron 8 mg IV bolus then 0.015 mg/kg/hour (≥18 years) or 0.15 mg/kg bolus then 0.03 mg/kg/hour (<18 years)	DB, PRO, RCT Patients 2-65 years old undergoing hematopoietic cell transplantation, in addition to dexamethasone	N=187 9 days	Primary: Number of emetic episodes Secondary: Mean nausea score, complete control over emesis as defined by no emetic episodes and major control over emesis as defined by 1-2 emetic episodes in 24 hours	Primary: There were no statistical differences between granisetron (0.73) and ondansetron (0.86) for episodes of emesis (*P*=0.32). Secondary: There were no statistical differences in the mean nausea scores between granisetron (1.17) and ondansetron (1.29; *P*=0.32). When stratified by age: there were no statistical differences in the <18 year old group between granisetron (0.54) and ondansetron (0.87) in mean episodes of emesis per day (*P*=0.08) or for mean nausea score per day (granisetron 0.82, ondansetron 1.14; *P*=0.09). There were no statistical differences in the ≥18 year old group between granisetron (0.80) and ondansetron (0.86) in mean episodes of emesis per day (*P*=0.71) or for mean nausea score per day (granisetron 1.29, ondansetron 1.36; *P*=0.65). There were no differences between granisetron and ondansetron in number of days in which emesis control was complete (*P*=0.68) or major (*P*=0.68).
Kalaycio et al[30] Granisetron 0.5 mg IV bolus then 1 mg/24 hour continuous infusion vs ondansetron 8 mg IV bolus then 24 mg/24 hour	DB, PRO, RCT Breast cancer patients receiving cyclophosphamide, thiotepa, and carboplatin, in addition to dexamethasone	N=45 7 days	Primary: Incidence and severity of nausea Secondary: Incidence of emesis, number of patients experiencing no	Primary: Incidence of nausea was no different between ondansetron and granisetron (*P*=0.86). Secondary: Incidence of emesis was not statistically different between granisetron and ondansetron (*P*=0.67). There was no statistical difference between the groups in regards to the number of patients experiencing no emetic episodes (granisetron 9.1% vs ondansetron 17.4%; *P*=0.67).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
continuous infusion			emetic episodes	There were no significant differences in adverse effects between granisetron and ondansetron.
Gralla et al[31] Ondansetron 32 mg IV vs palonosetron 0.25 mg IV vs palonsetron 0.75 mg IV	DB, PRO, RCT Patients receiving moderately emetogenic chemotherapy	N=570 5 days	Primary: Proportion of patients with no emetic episodes and no rescue medication (complete response) during the 24 hour period after chemotherapy (acute period) Secondary: Efficacy in treatment of delayed CINV (≤ 5 days post chemotherapy), overall tolerability	Primary: Complete response rates were significantly higher for palonosetron 0.25 mg (81.0%) than ondansetron (68.6%) during the acute period (*P*<0.01). Secondary: Complete response rates were significantly higher for palonosetron than ondansetron at 24-120 hours (74.1% vs 55.1%; *P*<0.01) and overall 0-120 hours (69.3% vs 50.3%; *P*<0.01). Complete response rates achieved with palonosetron 0.75 mg were numerically higher but not statistically different from ondansetron during all time intervals. Both treatments were well tolerated with adverse events reported in 16% of patients receiving palonosetron vs 13.9% of patients receiving ondansetron. Post hoc analysis revealed no differences in the duration of adverse events in patients treated with ondansetron vs palonosetron.
Aapro et al[32] Palonosetron 0.25 mg IV vs ondansetron 32 mg IV or dolasetron 100 mg IV	RETRO post hoc analysis of studies by Eisenberg et al[37] and Gralla et al[46] Patients ≥65 years receiving moderately emetogenic chemotherapy	N=171 5 days	Primary: Complete response during the acute period (0-24 hours after chemotherapy), delayed period (24-120 hours), and overall period (0-120 hours) with significance *P*≤	Primary: During the overall post chemotherapy period, complete response rate was significantly higher in the palonosetron group than in the ondansetron/dolasetron group (70.9% vs 51.2%; *P*=0.011). The proportion of patients with complete response during the acute time period was not significantly different between the palonosetron and ondansetron/dolasetron groups (84.8% vs 74.4%; *P*>0.025). Complete response was significantly higher in the palonosetron group compared to the ondansetron/dolasetron group during the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			0.025 Secondary: Not reported	delayed period (72.2% vs 53.5%; *P*=0.016). Secondary: Not reported
Davidson et al[33] Ondansetron 8 mg OT BID for 3 days vs ondansetron 8 mg ODT BID for 3 days	DB, MC, PRO, RCT Patients receiving cyclophosphamide	N=427 3 days	Primary: Complete or major control of emesis on their worst of days 1 through 3 Secondary: Not reported	Primary: Complete or major control of emesis was achieved by 80% of OT patients and 78% of ODT patients (90% CI, -8.6% to 4.4% with ±15% limit for equivalence). Complete control of emesis for days 1 through 3 was not significantly different between the treatment groups with 63% of OT and 64% of ODT patients. There was no significant difference in overall incidence of adverse effects between the 2 formulations. The most common adverse effects reported and those most frequently assessed as drug-related were headache (OT 11% vs ODT 9%) and constipation (both 10%). Secondary: Not reported
Likun et al[34] Palonosetron vs dolestron or granisetron or	MA of 8 RCTs Studies included patients ≥18 years of age and compared first-generation 5-HT_3 antagonists to palonosetron	N=3,592 Varied	Primary: Complete response of the acute, delayed, and overall phases of CINV after chemotherapy Secondary: Adverse effects of palonosetron	Primary: All eight RCTs compared palonosetron with first-generation 5-HT_3 antagonists for prevention of acute CINV. There was no heterogeneity between included studies (P=0.80). Meta-analysis that included 3,592 patients with 3,696 cycles showed that palonosetron reduced the risk of acute CINV by 24% (OR, 0.76; 95% CI, 0.66 to 0.88, P=0.0003). Subgroup analysis showed that there were statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.68; 95% CI, 0.56 to 0.83; P=0.0001) and 0.75 mg of palonosetron (OR, 0.82; 95% CI, 0.69 to 0.99; P=0.03). Seven RCTs with 3,384 patients (3,488 cycles) compared palonosetron with first-generation 5-HT_3 antagonists in prevention

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ondansetron				of delayed CINV. The results showed no heterogeneity (P=0.59) in any included studies (OR, 0.62; 95% CI, 0.54 to 0.71) in favor of palonosetron (P<0.00001). Subgroup analyses indicated statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51 to 0.75; P<0.00001) and 0.75 mg of palonosetron (OR, 0.61; 95% CI, 0.52 to 0.72; P<0.00001). Seven RCTs compared palonosetron with 5-HT_3 antagonists in prevention of the overall phase of CINV. Meta-analysis showed an OR of 0.64 (95% CI, 0.56 to 0.74) in favor of palonosetron (P<0.00001). Subgroup analysis showed statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51 to 0.75; P<0.00001) and 0.75 mg (OR, 0.65; 95% CI, 0.55 to 0.76; P<0.00001). There was no statistically significant differences between 0.25 and 0.75 mg of palonosetron in terms of preventing acute CINV (OR, 1.09; 95% CI, 0.85 to 1.38; P=0.50), delayed CINV (OR, 1.05; 95% CI, 0.83 to 1.32; P=0.68), or overall phase CINV (OR, 1.11; 95% CI, 0.88 to 1.40; P=0.38). Secondary: Seven RCTs reported constipation as an adverse event. Meta-analysis showed that palonosetron increased the risk of constipation by 39% (OR, 1.39; 95% CI, 1.08 to 1.78; P=0.01). Subgroup analyses showed significant differences between 0.75 mg of palonosetron and first-generation 5-HT_3 antagonists (P=0.04), but not between 0.25 mg of palonosetron and first-generation 5-HT_3 antagonists (P=0.20).
Radiation-Induced Nausea and Vomiting				
Spitzer et al[34] Granisetron 2 mg PO	DB, PG, PRO, RCT Patients ≥18 years diagnosed with	N=34 4 days	Primary: Number of patients who had 0 emetic	Primary: Significantly more patients given granisetron (33.3%) and ondansetron (26.7%) experienced no episodes of emesis than the historical control (0%; *P*<0.01 for both granisetron and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 8 mg PO vs historical control	malignant disease or aplastic anemia receiving 11 fractions of radiation over the course of 4 days		episodes over 4 days Secondary: Percent of patients with 0 emetic episodes and no rescue medication over 24 hours and 4 days	ondansetron compared to historical control). Secondary: During the first 24 hours, significantly more patients receiving granisetron (61.1%) and ondansetron (46.7%) had no emetic episodes than the historical control group (6.7%; *P*<0.01). Within the first 4 days, fewer patients in the granisetron (27.8%) and ondansetron groups (26.7%) had 0 emetic episodes and needed no rescue medication compared to historical controls (0%; *P*<0.01).
Postoperative Nausea and Vomiting				
Olutoye et al[36] Dolasetron 45 µg/kg IV vs dolasetron 175 µg/kg IV vs dolasetron 350 µg/kg IV vs dolasetron 700 µg/kg IV vs ondansetron 100 µg/kg IV	DB, PG, PRO, RCT Patients 2-12 years old receiving day surgery	N=204 Duration not specified	Primary: Complete response (no postoperative emetic symptoms) Secondary: Not reported	Primary: There were no significant differences in complete response between ondansetron 100 µg/kg, dolasetron 700 µg/kg and dolasetron 350 µg/kg. Ondansetron, dolasetron 700 µg/kg and dolasetron 350 µg/kg were all statistically better than dolasetron 175 µg/kg and dolasetron 45 µg/kg (*P*<0.05). Secondary: Not reported
Meyer et al[37] Dolasetron 12.5 mg IV	DB, PRO, RCT Patients undergoing day surgery	N=92 Duration not specified	Primary: Need for antiemetic rescue medication	Primary: The need for rescue antiemetic in the dolasetron group was 40% compared to the ondansetron group which was 70% (*P*<0.004).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 4 mg IV			Secondary: Evaluation of nausea and vomiting within 24 hours of surgery, overall time until discharge-ready in day surgery, overall time spent in PACU	Secondary: There was no significant difference between the two groups in regards to the number of patients who actually vomited (*P*=0.34). The overall time until discharge-ready in day surgery was 131 minutes for dolasetron and 158 minutes for ondansetron (*P*=0.17). The overall time spent in the PACU was similar between groups (*P*=0.99).
Walker[38] Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	RETRO Medical charts of patients who underwent total abdominal hysterectomy or laparoscopic cholecystectomy	N=59 24 hours	Primary: Number of recorded episodes of PONV in 24 hours after surgery, time to occurrence of PONV Secondary: Not reported	Primary: PONV occurred in 44% patients receiving dolasetron and 53% patients receiving ondansetron. Four patients (36%) receiving dolasetron experienced PONV in the first 2 hours after surgery, compared with 7 patients (39%) receiving ondansetron. Differences in primary end points did not reach statistical significance (*P* value not reported). Secondary: Not reported
Karamanlioglu et al[39] Dolasetron 1.8 mg/kg PO vs ondansetron 0.15 mg/kg PO vs	DB, PRO, RCT Children undergoing elective strabismus surgery, middle ear surgery, adenotonsillectomy or orchiopexy	N=150 Duration not specified	Primary: Nausea and vomiting rates, total nausea and vomiting score Secondary: Not reported	Primary: Over the 0-24 hour period, both dolasetron and ondansetron were significantly better than placebo in nausea (16% vs 26% vs 40%), vomiting (8% vs 16% vs 30%) and total nausea and vomiting scores (32% vs 48% vs 78%; *P*<0.05 compared to placebo) There were no significant differences between dolasetron and ondansetron (no *P* values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Medications were given 1 hour before induction of surgery.				
White et al[40] Granisetron 1 mg PO one hour before surgery vs ondansetron 4 mg IV at the end of surgery	DB, MC, PRO, RCT Patients undergoing laparoscopic surgery	N=220 24 hours post surgery	Primary: Postoperative episodes of emesis, patient report of nausea, need for rescue antiemetic medication Secondary: Not reported	Primary: PONV <4 hours post surgery: nausea was reported in 47% and 43% of ondansetron and granisetron patients, respectively. Vomiting was noted in 22% of both ondansetron and granisetron patients. Rescue antiemetics were used in 34% and 39% of ondansetron and granisetron patients, respectively. PONV 4-24 hours post surgery: nausea was reported in 46% and 38% of ondansetron and granisetron patients, respectively. Vomiting was noted in 23% and 13% of ondansetron and granisetron patients, respectively. Rescue antiemetics were used in 25% and 24% of ondansetron and granisetron patients, respectively. None of these comparisons were significantly different from each other (*P* values not given). Secondary: Not reported
Gan et al[41] Granisetron 0.1 mg IV and dexamethasone 8 mg IV vs ondansetron 4 mg IV and dexamethasone 8 mg IV	DB, MC, PG, PRO, RCT Patients undergoing abdominal hysterectomy, medications given 15 minutes prior to end of surgery	N=176 24 hours post surgery	Primary: Proportion of patients with no vomiting during 0-2 hours post surgery Secondary: Proportion of patients with no vomiting during	Primary: From 0-2 hours post surgery, the granisetron group had no emesis in 94% of patients and the ondansetron group had no emesis in 97% of patients. The difference was not statistically significant (95% CI, -8.5 to 3.8). Secondary: From 0-6 hours post surgery, the granisetron group had no emesis in 87% of patients and the ondansetron group had no emesis in 93% of patients. This difference was not statistically significant (95% CI, -14.6 to 2.8).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			0-6 hours and overall 0-24 hours post surgery	From 0-24 hours post surgery, the granisetron and ondansetron groups had no emesis in 83% and 87% of its patients, respectively. The difference was not statistically significant (95% CI, -14.4 to 6.9).
Gan et al[42] Ondansetron ODT 8 mg before discharge and 12 hours later vs placebo ODT	DB, PC, PRO, RCT Patients undergoing outpatient gynecological laparoscopy	N=60 24 hours post surgery	Primary: Incidence of PONV, severity of nausea, rescue antiemetic, side effects, satisfaction PONV manage-ment assessed at 2 and 24 hours post surgery Secondary: Not reported	Primary: Ondansetron ODT patients had significantly less post discharge emesis (3% vs 23%), and less severe nausea after discharge compared to placebo patients (P<0.05). The ondansetron ODT group was more satisfied with PONV control than placebo (90% vs 63%; P<0.05). Ondansetron ODT was less acceptable to patients although they would use it again (P<0.01). Patients rated the taste of ondansetron ODT less favorably than the placebo ODT. Secondary: Not reported
Loewen et al[43] 5-HT_3 antagonists (dosages and routes were not specified) vs traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol)	MA Review of randomized, double-blind, controlled clinical trials published in English and in MEDLINE or EMBASE from 1966-October 1999	41 trials met criteria 5-HT_3 antagonists N=2,855 and traditional agents N=3,783	Primary: Postoperative nausea and vomiting that occurred within 48 hours after surgery Secondary: 5-HT_3 receptor antagonists compared to traditional antiemetics for	Primary: 5-HT_3 receptor antagonists showed a 46% reduction in the odds of PONV (OR, 0.54; 95% CI, 0.42 to 0.71; P<0.001). 5-HT_3 receptor antagonists showed a 39% reduction in PONV over droperidol (OR, 0.61; 95% CI, 0.42 to 0.89; P<0.001). 5-HT_3 receptor antagonists showed a 56% reduction in PONV over metoclopramide (OR, 0.44; 95% CI, 0.31 to 0.62; P<0.001). Secondary: 5-HT_3 receptor antagonists showed a 38% reduction in vomiting compared to traditional antiemetics (OR, 0.62; 95% CI, 0.48 to 0.81; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			rates of vomiting	5-HT_3 antagonists showed a beneficial effect over droperidol in rate of vomiting (OR, 0.56; 95% CI, 0.41 to 0.76; *P*<0.001). 5-HT_3 antagonists showed a beneficial effect over metoclopramide in rate of vomiting (OR, 0.50; 95% CI, 0.32 to 0.77; *P*<0.001). Sedation was more common in the traditional group (11.9%) compared to 5-HT_3 receptor antagonists (5.6%; OR, 0.7; 95% CI, 0.32 to 0.64; *P*<0.001). Headache was more common in the 5-HT_3 receptor antagonist group (17.0%) than in the traditional antiemetic group (13.0%; OR, 1.65; 95% CI, 1.35 to 2.02; *P*<0.001).
Eberhart, et al[44] Dolasetron 12.5 mg IV vs droperidol 10 µg/kg IV vs dolasetron 12.5 mg and droperidol 10 µg/kg IV vs placebo	DB, PG, RCT Patients undergoing vitreoretinal surgery received study medication 5-10 minutes before the end of surgery	N=304 Duration not specified	Primary: Mean PONV score (0-3, with 0 being no nausea or vomiting) with a significance level of *P*=0.01 Secondary: Complete prevention of PONV	Primary: Droperidol was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Dolasetron was numerically better but not statistically better than placebo (*P*=0.017). Combination therapy was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Droperidol and dolasetron were not statistically different from each other (*P*=0.096), although droperidol was numerically better in the reduction of mean PONV score. Secondary: Droperidol was statistically better than placebo (*P*<0.0006) in complete prevention of PONV. Dolasetron was numerically better but not statistically better than placebo (*P*=0.038). Combination therapy was statistically better than placebo (*P*<0.0001) in complete prevention of PONV. Droperidol and dolasetron were not statistically different from each other (*P*=0.17) although droperidol was numerically better in complete prevention of PONV.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hamid et al[45] Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg IV vs placebo All were given at induction of anesthesia.	DB, PC, PRO, RCT Children 2-10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed during the first 24 hours post surgery Secondary: Not reported	Primary: The incidence of POV during the first 24 hours after surgery in the ondansetron group (42%) was significantly less than in the dimenhydrinate (79%; *P*<0.02) and placebo (82%; *P*<0.01) groups. The number of episodes of POV in the first 24 hours differed significantly between the ondansetron and placebo groups only. The number of children whose discharges from hospital were delayed secondary to POV in the ondansetron group (0 of 25) was significantly less than in the placebo group (4 of 22; *P*<0.04) Secondary: Not reported
Kothari et al[46] Dimenhydrinate 50 mg IV vs ondansetron 4 mg IV All medications were administered before induction of anesthesia.	DB, PRO, RCT Consecutive patients undergoing laparoscopic cholecystectomy	N=128 24 hours after discharge	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea and vomiting, frequency of PONV 24 hours after discharge Secondary: Not reported	Primary: Need for rescue medication occurred in 34% of ondansetron group and 29% of dimenhydrinate group (*P*=0.376). Postoperative vomiting occurred in 6% of ondansetron group and 12% of dimenhydrinate group (*P*=0.228). Postoperative nausea and vomiting occurred in 42% of ondansetron group and 34% of dimenhydrinate group (*P*=0.422). One patient in the ondansetron group and 2 patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (*P*=not significant). Rates of postoperative nausea and vomiting 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10% and 14%; *P*=0.397 and 2% and 5%; *P*=0.375, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
McCall et al[47] Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg vs placebo Study drugs were given at the end of surgery and again 4 hours later.	DB, PC, PRO, RCT Patients with a mean age of 11.8 years undergoing reconstructive burn surgery with general anesthesia	N=100 8 hours	Primary: Incidence of PONV, POV Secondary: Not reported	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, as compared with the results of patients who received placebo. POV was reduced from 61% in the placebo group to 29% and 40% in the ondansetron and dimenhydrinate groups, respectively, and PONV was similarly reduced from 69% to 47% and 40%, respectively. The differences between ondansetron and dimenhydrinate were not statistically significant. Secondary: Not reported
Van den Berg[48] Prochlorperazine 0.2 mg/kg IM vs prochlorperazine 0.2 mg/kg IV vs ondansetron 0.06 mg/kg IV vs placebo All were given with induction of anesthesia.	DB, PRO, RCT Patients from 9-61 years of age received standardized general anesthesia for tympanoplasty	N=148 24 hours	Primary: Incidence of retching and vomiting in the PACU during first 24 hours post surgery Secondary: Postoperative headache	Primary: Nausea alone during the first 24-hour postoperative period was infrequent in each treatment group with a similar incidence (3%-8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11%-24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was not significant ($P>0.05$ for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of patients in the placebo group, 16% in those given prochlorperazine IM ($P<0.0005$), 19% in those given ondansetron IV ($P<0.0005$) and 30% in those given prochlorperazine IV ($P<0.05$). The study was not powered to detect a difference between active treatment groups. The percent of patients who experienced no nausea or vomiting

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was 27% for placebo, 57% for prochlorperazine IM, 43% for prochlorperazine IV, and 62% for ondansetron IV. Only the prochlorperazine IM and ondansetron IV groups achieved significance compared to placebo (*P*<0.01 and *P*=0.005, respectively). Secondary: Incidence of headache reported in the first 24 hours after surgery (placebo 56%, prochlorperazine IM 41%, prochlorperazine IV 43% and ondansetron IV 49%) was similar in the four groups.
Chen et al[49] Prochlorperazine maleate 10 mg IM vs ondansetron 4 mg IV All were administered at end of surgical procedure.	DB, RCT Patients greater than 17 years old undergoing elective, primary or revisionary total hip or total knee replacement procedures	N=78 48 hours postoperatively	Primary: Incidence and severity of PONV Secondary: Number of rescue antiemetic doses required, number of physical therapy cancellations because of PONV, length of hospital stay	Primary: The incidence of nausea was significantly greater in the ondansetron group compared with the prochlorperazine group (*P*=0.02), as was the severity of nausea (*P*=0.04). The incidence (*P*=0.13) and severity (*P*=0.51) of vomiting were similar between the two groups. Secondary: The need for rescue antiemetic therapy was greater in the ondansetron group compared to the prochlorperazine group, but the difference was not statistically significant (*P*=0.08). The mean number of rescue antiemetic doses required was 2.1 in the ondansetron group and 1.7 in the prochlorperazine group, but the difference did not reach statistical difference (*P*=0.50).
Erhan et al[50] granisetron 3 mg IV vs ondansetron 4 mg IV vs	DB, PC, PRO, RCT Patients between the ages of 21-75 years with an ASA physical class of I-II, scheduled for laparoscopic cholecystectomy	N=80 Monitored over 24 hour time period	Primary: Complete response (no postoperative emetic symptoms) Secondary: Not reported	Primary: The occurrence of nausea and vomiting for the different groups were: ondansetron (35%), granisetron (30%), dexamethasone (25%) and placebo (75%). All *P* values were less then 0.05 for comparisons to placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dexamethasone 8 mg IV vs placebo	with general anesthesia			
Kovac et al[51] palonosetron 0.025 mg IV vs palonsetron 0.050 mg IV vs palonsetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, RCT Female patients with an ASA status I-III, greater than 18 years old, scheduled to undergo elective inpatient gynecological or breast surgery that was expected to last a minimum of 1 hour and were scheduled to be hospitalized for at least 72 hours after surgery	N=544 Monitored over 72 hour time period	Primary: Complete response (no postoperative emetic symptoms) over 0-24 hours and 24-72 hours Secondary: Time to treatment failure, use of rescue therapy, emetic episodes, nausea and safety	Primary: Compared to placebo (36%), complete response was 46% for palonosetron 0.025 mg (*P*=0.069), 47% for palonosetron 0.05 mg (*P*=0.069) and 56% for palonsetron 0.075 mg (*P*=0.001) when evaluated at the 0-24 hour time interval after surgery. Complete response for placebo and palonosetron 0.075 mg were 52% and 70% for the 24-74 hour time interval (*P*=0.002). Complete response rates for palonosetron 0.025 mg and 0.050 mg were not statistically different than placebo. Secondary: A significantly longer time to treatment failure was observed in the palonosetron 0.075 mg group vs placebo (*P*=0.004). No significant time difference was seen between placebo and palonosetron 0.025 mg group (*P*=0.112) and palonosetron 0.05 mg group (*P*=0.060). During the 0-72 hour study period 62/136 (46%) placebo patients compared to 36/135 (27%) palonosetron 0.075 mg patients required rescue medication (*P*<0.001). During the 0-24 hour time block 82/136 (60%) placebo patients compared to 54/136 (46%) palonsetron 0.075 mg patients experience an emetic episode (*P*<0.001). During the 24-72 hour time block there was no significant difference between the placebo (10%) and palonosetron 0.075 mg groups (4%; *P*=0.061). During the 0-24 hour time block significantly fewer patient treated with palonosetron 0.075 mg (50%) compared to placebo (71%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				experienced nausea (*P*<0.001). All doses of palonosetron were well tolerated in this study. Percentages of severe adverse events were 5% in the placebo group, 4% in the palonosetron 0.075 mg group, and 7% in both the palonosetron 0.025 mg and 0.05 mg groups. Not all values were reported in secondary end points.
Candiotti et al[52] Palonosetron 0.025 mg IV vs palonosetron 0.05 mg IV vs palonsetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, RCT Patients at least 18 years old with an ASA physical status of I-III and scheduled to undergo elective laparoscopic abdominal or gynecological surgery and had to have at least two of the following risk factors: female gender, history of PONV and/or motion sickness, or nonsmoking status	N=546 Monitored over 72 hour time period	Primary: Complete response (no postoperative emetic symptoms) over 0-24 hours and 24-72 hours Secondary: Emetic episodes, nausea, interference of PONV with patient functions and safety	Primary: Complete response at 0-24 hours was 26% in the placebo group compared with 33% of the palonsetron 0.025 mg group (*P*=0.187), 39% in the palonosetron 0.050 mg group (*P*=0.017) and 43% in the palonosetron 0.075 mg group (*P*=0.004). Complete response at 24-72 hours was 41% in the placebo group compared to 44% in the palonsetron 0.025 mg group (*P*=0.638), 47% in the palonosetron 0.050 mg group (*P*=0.249) and 49% in the palonosetron 0.075 mg group (*P*=0.188). Secondary: Emetic episodes at 0-72 hours were 33% in the palonosetron 0.075 mg group compared to 44% in the placebo group(*P*=0.075). During the 0-24 hour time period more patients receiving palonosetron 0.075 mg did not experience nausea (*P*=0.033) or experienced less intense nausea (*P*=0.0504) compared to placebo. Total Osoba questionnaire scores (evaluating interference of PONV with patient function) were better with palonosetron 0.075 mg than placebo (*P*=0.004). Adverse events were reported in 7% of patients in the palonosetron 0.075 mg group and 10% in placebo group (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Only values of palonosetron 0.075 mg group were reported for the secondary end points.

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, ODT=orally disintegrating tablet, OT=oral tablet, PO=by mouth
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-labeled, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover
Miscellaneous abbreviations: ASA=American Society of Anesthesiologist, CINV=chemotherapy-induced nausea and vomiting, ECOG=Eastern Cooperative Oncology group, FLIE= Functional Living Index- emesis, MNS=mean nausea score, PACU=post anesthesia care unit, PONV=postoperative nausea and vomiting, POV=postoperative vomiting, RINV=radiation-induced nausea and vomiting

Special Populations

Table 5. Special Populations [1-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Dolasetron	Controlled clinical studies did not include sufficient numbers of elderly patients to determine whether they respond differently than younger adult patients. FDA-approved for use in children ≥2 years of age.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Unknown; use with caution.
Granisetron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Injection, tablet: FDA-approved for use in children ≥2 years of age. Patch: Safety and efficacy in children have not been established.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Unknown; use with caution.
Ondansetron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. CINV: FDA-approved for use in children ≥6 months of age (injection) or ≥4 years of age (oral formulations). There is no experience with the use of a 24 mg dosage in pediatric patients. RINV: FDA-approved for use in children ≥1 month of age (injection). Safety and efficacy in children	Renal dose adjustment not required.	In severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed 8 mg per day.	B	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established (oral formulations). PONV: Safety and efficacy in children have not been established.				
Palonosetron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. FDA-approved for use in children ≥1 month of age (CINV only). Safety and efficacy for PONV in children have not been established.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Unknown; use with caution.
Combination Product					
Netupitant/ palonosetron	Controlled clinical studies did not include sufficient numbers of elderly patients to determine whether they respond defiantly than younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment not required for mild or moderate impairment (CrCl≥30). Data is limited for severe renal impairment and end-stage renal disease.	Hepatic dose adjustment not required for mild to moderate impairment (Child-Pugh score 5 to 8). Data is limited for severe hepatic impairment.	C	Unknown; use with caution.

CINV=chemotherapy-induced nausea/vomiting, CrCl=creatinine clearance, PONV=postoperative nausea/vomiting, RINV=radiation-induced nausea/vomiting

Adverse Drug Events

Table 6. Adverse Drug Events (%) Reported with the Single Entity 5-HT$_3$ Receptor Antagonists[1-10]

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron	Netupitant/ palonosetron
Cardiovascular					
Bradycardia	4-5.1	4.5	6	1-4	-
Hypertension	2.9	2-2.6	2.5	<1	-
Hypotension	5.3	3.4	3-5	1	-
Tachycardia	2.2-3	-	-	1	-
Central Nervous System					
Anxiety	-	3.4	6	1	-

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron	Netupitant/ palonosetron
Chills/shivering	2.0	5	7	-	-
Dizziness	2.2-5.5	4.1	4-7	1	-
Drowsiness	2.4	-	20	-	-
Headache	9.4-24.3	8.6	9-27	3-9	9
Insomnia	-	4.9	-	<1	-
Malaise/fatigue	3.4	-	9-13	<1	4 to- 7
Paresthesia	-	-	2	-	-
Somnolence	-	4	-	<1	-
Dermatological					
Pruritus	3.1	-	2-5	-	-
Skin rashes	-	1	-	<1	-
Endocrine and Metabolic					
Increased AST and ALT	3.6	5.6	3.4	<1	-
Gastrointestinal					
Abdominal pain	3.2	6	3	<1	-
Constipation	-	3-9.4	6-9	2-5	3
Diarrhea	12.4	3.4-4	4-7	1	-
Dyspepsia	2.2-3	3.0	-	<1	4
Flatulence	-	3	-	<1	-
Xerostomia	-	-	2	<1	-
Genitourinary					
Oliguria	2.6	2.2	-	-	-
Urinary retention	2	-	3-5	<1	-
Urinary tract infection	-	2.6	-	-	-
Musculoskeletal					
Asthenia	-	5	-	-	8
Other					
Anemia	-	9.4	-	-	-
Cold sensation	-	-	2	-	-
Coughing	-	2.2	-	-	-
Fever/pyrexia	3-4.3	7.9-8.6	2-8	<1	-
Gynecological disorder	-	-	6-7	-	-
Hypoxia	-	-	9	-	-
Injection site reaction	-	-	4	-	-
Leukocytosis	-	3.7	-	-	-
Pain	2.4	10.1	2	-	-
Taste disorder	-	2	-	-	-
Weakness	-	-	2	1	-
Wound problems	-	-	11-28	-	-

ALT=alanine aminotransferase, AST=aspartate aminotransferase
- Event not reported or incidence <1%.

Contraindications:
The use of any serotonin-3 antagonists is contraindicated in patients with known hypersensitivity to the drug or any of its components.[1-10] Dolasetron injection is contraindicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy due to dose

dependent QT prolongation.[4] All ondansetron products are contraindicated with concomitant use of apomorphine due to reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.[6-8]

Warnings and Precautions:

Table 7. Warnings and Precautions[1-10]

Warnings/Precautions	Dolasetron	Granisetron	Ondansetron	Palonosetron	Netupitant/ palonosetron
Cardiovascular events; QT prolongation reported, use with caution in patients with pre-existing arrhythmias		a			
Gastric or Intestinal Peristalsis; use in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention. Use does not stimulate gastric or intestinal peristalsis, do not use instead of nasogastric suction		a	a		
PR and QRS Interval Prolongation; reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients; use caution in patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia or patients receiving drugs known to prolong the PR interval and QRS interval	a				
QTc Interval Prolongation; Torsade de Pointes has been reported, avoid use in patients with long QT syndrome, hypokalemia or hypomagnesemia	a		a		
Serotonin Syndrome has been reported; avoid use with concomitant use of serotonergic drugs	a	a	a	a	a
Skin reactions, mild were reported; discontinue if severe		a (patch)			
Sunlight exposure; cover patch with clothing to avoid drug being affected		a (patch)			

Drug Interactions

Table 8. Drug Interactions[1-10]

Generic Name	Interacting Medication or Disease	Potential Result
5-HT3 antagonists	Serotonergic drugs (e.g., SSRIs, SNRIs)	Serotonin syndrome may occur
5-HT3 antagonists	Drugs known to prolong the QT interval and/or are arrhythmogenic	Coadministration may result in clinical consequences.
Single Entity Products		
Dolasetron	Atenolol	Clearance of dolasetron active metabolite may decrease.
Dolasetron	Cimetidine	Systemic exposure and maximum plasma concentration of dolasetron active metabolite may increase.

Generic Name	Interacting Medication or Disease	Potential Result
Dolasetron, ondansetron	Rifamycins (rifabutin, rifampin, rifapentine)	Systemic exposure and maximum plasma concentration of dolasetron active metabolite may decrease.
Dolasetron	Ziprasidone	A possible additive or synergistic prolongation of the QT interval may occur.
Granisetron injection	Phenobarbital	Clearance of intravenous granisetron increased; clinical significance is unknown.
Ondansetron	Apomorphine	Profound hypotension and loss of consciousness when administered together. Use is contraindicated.
Combination Products		
Netupitant/ palonosetron	Drugs metabolized via CYP3A4 (including midazolam and benzodiazepines)	Plasma concentrations of CYP3A4 substrates can increase when co-administered and the inhibitory effects can last for several days.
Netupitant/ palonosetron	CYP3A4 inducers (such as rifampin)	Avoid use of netupitant/palonosetron in patients who are chronically using a strong CPY3A4 inducer due to reduced efficacy of the netupitant component.
Netupitant/ palonosetron	CYP3A4 inhibitors (such as ketoconazole)	Concomitant use of netupitant/palonosetron in patients using a strong CYP3A4 inhibitor can significantly increase systemic exposure of netupitant. However, no change is needed for a single dose.
Netupitant/ palonosetron	Dexamethasone	A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant (not studied past 4 days); administer a reduced dose of dexamethasone when co-administered.

Dosage and Administration

Table 9. Dosing and Administration[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Dolasetron	Postoperative Nausea and Vomiting (PONV) prophylaxis and treatment (age 17 or older): Solution for injection: 12.5 mg x1 dose Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 17 or older): Tablet: 100 mg x1 dose within 1 hour of chemo	Postoperative Nausea and Vomiting (PONV) prophylaxis and treatment (age 2 to 16): Solution for injection: 0.35 mg/kg (max 12.5 mg) x1 dose Solution for injection (as an oral dose): 1.2 mg/kg (max 100 mg) x1 dose mixed in apple or apple-grape juice within 2 hours before surgery Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 2 to 16): Tablet: 1.8 mg/kg (max 100 mg) x1 dose within 1 hour of chemo	Tablet: 50 mg 100 mg Solution for IV injection, vial: 12.5 mg/0.625 mL 100 mg/5 mL 500 mg/25 mL
Granisetron	Chemotherapy-Induced	Chemotherapy-Induced	Solution for injection,

Generic Name	Adult Dose	Pediatric Dose	Availability
	Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Tablet: 2 mg x1 dose, 1 hour before chemo or 1 mg x1 dose 1 hour before chemo, then 1 mg x1 dose 12 hours later on chemo days Patch: apply 1 patch to outer arm a minimum of 24 hours before chemo (max 48 hours before), leave on for 24 hours after chemo (max 7 days depending on duration of chemo regimen) Solution for injection (age 17 or older): 10 mcg/kg IV x1 dose within 30 minutes before starting chemo on chemo days Radiation-Induced Nausea and Vomiting (RINV) prophylaxis: Tablet: 2 mg x1 dose up to 1 hour before radiation	Nausea and Vomiting (CINV) prophylaxis (age 2 to 16): Solution for injection: 10 mcg/kg IV x1 dose within 30 minutes before starting chemo on chemo days Radiation-Induced Nausea and Vomiting (RINV) prophylaxis: Safety and effectiveness has not been established.	vial: 1 mg/1 mL 4 mg/4 mL 0.1 mg/1 mL Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours
Ondansetron	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Solution for injection: 0.15 mg/kg IV (max 16 mg/dose) over 15 minutes starting 30 minutes before chemo then every four to eight hours after the first dose ODT, oral film, oral solution, tablet (highly emetogenic): 24 mg x1 dose 30 minutes before start of therapy ODT, oral film, oral solution, tablet (moderately emetogenic): 8 mg twice daily, 30 minutes before chemo and 8 hours later followed by 8 mg twice daily for one to two days after completion of chemo Radiation-Induced Nausea	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis: Injection (6 months to 17 years): refer to adult dosing ODT, oral film, oral solution, tablet (highly emetogenic): Safety and effectives has not been established. ODT, oral film, oral solution, tablet (moderately emetogenic; age 12 to 17): refer to adult dosing ODT, oral film, oral solution, tablet (moderately emetogenic; age 4 to 11): 4 mg TID, 30 minutes before chemo and then 4 and 8 hours later followed by 4 mg three times a day for one to two days after completion of	ODT: 4 mg 8 mg Oral film: 4 mg 8 mg Solution: 4 mg/5 mL Solution for injection, vial: 4 mg/2 mL 40 mg/20 mL Tablet: 4 mg 8 mg 24 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	and Vomiting (RINV) prophylaxis: Tablet, oral film, oral solution, ODT (total body irradiation): 8 mg x1 dose 1 to 2 hours before each fraction of radiotherapy each day Tablet, oral film, oral solution, ODT (single high-dose fraction to the abdomen): 8 mg x1 dose 1 to 2 hours before radiotherapy Tablet, oral film, oral solution, ODT (daily fractionated to the abdomen): 8 mg x1 dose 1 to 2 hours before radiotherapy then every 8 hours after the first dose for each day radiotherapy is given Postoperative Nausea and Vomiting (PONV) prophylaxis or treatment (age 18 or older): Solution for injection: 4 mg x1 dose IV in not less than 30 seconds (preferably over two to five minutes) immediately before induction or as soon as nausea starts Postoperative Nausea and Vomiting (PONV) prophylaxis (age 18 or older): ODT, oral film, oral solution, tablet: 16 mg x1 dose 1 hour before induction of anesthesia	chemo Radiation-Induced Nausea and Vomiting (RINV) prophylaxis: Safety and effectiveness has not been established. Postoperative Nausea and Vomiting (PONV) prophylaxis or treatment: Solution for injection (age 12 to 17): refer to adult dosing Solution for injection (age 1 month to 11 years): 0.1 mg/kg (<40 kg) or 4 mg (≥40 kg) x1 dose	
Palonosetron	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Solution for injection: 0.25 mg x1 dose IV over 30 seconds, 30 minutes before start of chemo Postoperative Nausea and Vomiting (PONV) prophylaxis (age 18 or older): Solution for injection: 0.075 mg x1 dose IV over 10 seconds, immediately before anesthesia	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 1 month to 17 years): Solution for injection: 20 mcg/kg (max 1.5 mg) x1 dose IV over 15 minutes, 30 minutes before start of chemo Postoperative Nausea and Vomiting (PONV) prophylaxis: Safety and effectiveness has	Solution for IV injection, vial: 0.25 mg/5 mL 0.075mg/1.5 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	induction	not been established.	
Netupitant/ palonosetron	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Capsule: 300/0.5 mg x1 dose approximately 30 minutes before start of chemo	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis: Safety and effectiveness has not been established.	Capsule: 300/0.5 mg

BID=twice daily, CINV=chemotherapy-induced nausea and vomiting, IV=intravenous, ODT=orally disintegrating tablet, PO=oral, PONV=postoperative nausea and vomiting, QD=once daily, RINV=radiation-induced nausea and vomiting, TID=three times daily

Clinical Guidelines

Table 10. Clinical Guidelines Using the Single Entity 5-HT$_3$ Receptor Antagonists

Clinical Guideline	Recommendations
National Comprehensive Cancer Network (NCCN) **Clinical Practice Guidelines in Oncology: Antiemesis (2014)**[11]	For high emetic risk intravenous (IV) chemotherapy the following is recommended: · Combination of a neurokinin 1 (NK-$_1$) receptor antagonist, dexamethasone and any serotonin (5-HT$_3$) antagonist. · Lorazepam, a histamine (H$_2$) receptor blocker or proton pump inhibitor (PPI) may be given. **OR** · Combination of olanzapine, palonosetron and dexamethasone may be given with or without lorazepam, an H$_2$ receptor blocker or a PPI. For moderate emetic risk IV chemotherapy the following is recommended for *Day 1*: · Combination of dexamethasone and a 5-HT$_3$ antagonist (palonosetron preferred) with or without a NK-$_1$ receptor antagonist. · Lorazepam, an H$_2$ receptor blocker or PPI may be given. **OR** · Combination of olanzapine, palonosetron and dexamethasone may be given with or without lorazepam, an H$_2$ receptor blocker or a PPI. For moderate emetic risk IV chemotherapy the following is recommended for *Days 2 to 3*: · A 5-HT$_3$ antagonist as monotherapy (unless palonosetron used on Day 1); **OR** · Dexamethasone as monotherapy; **OR** · A NK-$_1$ receptor antagonist with or without a steroid; **OR** · Olanzapine given days two through four (if given day one). · Lorazepam may be added on to the regimen. · An H$_2$ receptor blocker or PPI may be given. For low emetic risk IV chemotherapy the following is recommended: · Dexamethasone; **OR** · Metoclopramide PRN; **OR** · Prochlorperazine PRN (maximum 40 mg/day); **OR** · Dolasetron, granisetron or ondansetron; **OR** · Lorazepam PRN; **OR**

Clinical Guideline	Recommendations
	· H_2 blocker or PPI For oral chemotherapy with moderate to high emetic risk the following is recommended*:* · A 5-HT_3 antagonist (dolasetron, granisetron or ondansetron) · Lorazepam may be given. · An H_2 receptor blocker or PPI may be given.
Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO): **Antiemetic Guideline (2013)**[12]	For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk or a regimen of anthracycline plus cyclophosphamide the following is recommended*:* · A three-drug regimen of single doses of a 5-HT_3 receptor antagonist, dexamethasone and oral aprepitant 125 mg (or fosaprepitant 150 mg IV). · For delayed emesis, it is recommended to give aprepitant 80 mg once daily for two days after chemotherapy (or none if fosaprepitant is used on Day 1). For the prevention of acute nausea and vomiting following chemotherapy of moderate emetic risk the following is recommended*:* · Palonosetron plus a single IV dose of dexamethasone 8 mg. For the prevention of acute nausea and vomiting following chemotherapy of low emetic risk the following is recommended*:* · A single antiemetic such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide. For the prevention of acute nausea and vomiting following chemotherapy of minimal emetic risk the following is recommended*:* · No antiemetic should be routinely administered to individuals without a history of nausea and vomiting. *F*or patients receiving multiple-day cisplatin the following is recommended*:* · A 5-HT_3 receptor antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. · The addition of an NK-$_1$ receptor antagonist (aprepitant or fosaprepitant) could be considered starting no later than day three (optimal administration schedule not defined).
American Society of Clinical Oncology Clinical Practice: **Guideline Update-Emesis (2011)**[13]	For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk the following is recommended*:* · A three-drug combination of a NK-$_1$ receptor antagonist (Days 1 through 3 for aprepitant; Day 1 only for fosaprepitant), a 5-HT_3 receptor antagonist (Day 1 only) and dexamethasone (Days 1 through 3 or Days 1 through 4). For the prevention of acute nausea and vomiting following chemotherapy of moderate emetic risk the following is recommended*:* · A two-drug combination of palonosetron (Day 1 only) and dexamethasone (Days 1 through 3). If palonosetron is not available, may substitute a first-generation 5-HT_3 receptor antagonist (preferably granisetron or ondansetron). · There is limited evidence that supports adding aprepitant to the combination.

Clinical Guideline	Recommendations
	For the prevention of acute nausea and vomiting following chemotherapy of low emetic risk the following is recommended: · A single 8 mg dose of dexamethasone before chemotherapy. For the prevention of acute nausea and vomiting following chemotherapy of minimal emetic risk the following is recommended: · No antiemetic should be administered routinely to individuals before or after chemotherapy.
Pediatric Oncology Group of Ontario: **Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients (2012)**[14]	Acute antineoplastic-induced (high emetic risk) nausea and vomiting · Children ≥12 years old and receiving antineoplastic agents of high emetic risk which are not known or suspected to interact with aprepitant receive: ondansetron or granisetron + dexamethasone + aprepitant. · Children ≥12 years old and receiving antineoplastic agents of high emetic risk which are known or suspected to interact with aprepitant receive: ondansetron or granisetron + dexamethasone. · Children <12 years old and receiving antineoplastic agents of high emetic risk receive: ondansetron or granisetron + dexamethasone. Acute antineoplastic-induced (moderate emetic risk) nausea and vomiting · Ondansetron or granisetron + dexamethasone is recommended Acute antineoplastic-induced (low emetic risk) nausea and vomiting · Ondansetron or granisetron is recommended Acute antineoplastic-induced (minimal emetic risk) nausea and vomiting · No routine prophylaxis is recommended Role of aprepitant in children receiving antineoplastic therapy: · Use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. · There is no evidence to support the safe and effective use of aprepitant in younger children.
The International Anesthesia Research Society: **Consensus Guidelines for Managing PONV (2003)**[15]	· 5-HT_3 receptor antagonists are recommended for prophylaxis of postoperative nausea and vomiting (PONV) and studies have shown no difference in the safety and efficacy profile of any of the agents in this class. · Small-doses of 5-HT_3 receptor antagonists are recommended for the treatment of PONV in patients who did not receive prophylactic treatment. · Small-doses of 5-HT_3 receptor antagonists are recommended in patients when prophylaxis with dexamethasone fails to prevent PONV, but when a 5-HT_3 receptor antagonist fails as prophylaxis, another 5-HT_3 receptor antagonist should not be used as rescue therapy within the first 6 hours after surgery. · If PONV occurs more than 6 hours after surgery, repeat dosing of 5-HT_3 receptor antagonists may be considered.
Society of Obstetricians and Gynecologists of Canada Clinical Practice Guidelines:	· Ondansetron may be safe to use during the first trimester of pregnancy. Due to its limited effectiveness data, it should not be used as a first-line agent.

Clinical Guideline	Recommendations
The Management of Nausea and Vomiting of Pregnancy (2002)[16]	
American College of Obstetricians and Gynecologists (ACOG): **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy (2004)[17]**	· Patients who are taking a multivitamin at the time of conception may experience less nausea and vomiting during pregnancy. · First-line therapy is vitamin B6 (pyridoxine) with or without doxylamine (this combination product is no longer available in the United States, but the individual components are available). · Pharmacological therapy that is considered safe and efficacious in pregnancy includes antihistamines, phenothiazines, and benzamides (trimethobenzamide). · Severe nausea and vomiting of pregnancy or hyperemesis gravidarum may be treated with methylprednisolone as a last resort. · The use of 5-HT_3 receptor antagonists in pregnancy is controversial, though ondansetron may be used as an alternative to methylprednisolone. In practice the use of 5-HT_3 receptor antagonists in pregnancy appears to by increasing.

Conclusions

Treatment of chemotherapy- or radiation-induced nausea and vomiting generally involves the use of multiple agents that affect different receptor types, such as a dopamine antagonist, a corticosteroid and a 5-HT_3 receptor antagonist. Choice of agents generally depends upon the relative emetogenic potential of the regimen. When choosing among a class of agents, guidelines have suggested that all 5-HT_3 receptor antagonists can be appropriately dosed to provide equivalent efficacy, although some studies have suggested that palonosetron may be more effective the first-generation agents for moderately emetogenic chemotherapy.[22-52]

In terms of pharmacokinetics, palonosetron has a longer half-life that the other 5-HT_3 receptor antagonists.[9] Granisetron tablets and oral formulations of ondansetron are indicated for the treatment of radiation-induced nausea and vomiting (RINV).Dolasetron injection, ondansetron and palonosetron are also indicated for the treatment of postoperative nausea and vomiting (PONV).[1-10] The most common side effects of the 5-HT_3 receptor antagonists are constipation, headache, and asthenia, and the side effect profiles appear comparable. Safety and efficacy of granisetron patch and netupitant/palonosetron in children have not been established, while the other 5-HT_3 receptor antagonists are approved for the use in children in certain indications.[1-10] Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically. All of the single entity 5-HT_3 receptor antagonists are available by injection and all but palonosetron are currently available by the oral route. In addition, Granisetron is formulated as a transdermal patch and Netupitant/palonosetron is formulated as an oral capsule.[1-10]

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