# 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 2018*).
- 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, 2018; Hesketh 2017[a]*).
- Normal function of the upper GI tract involves interactions between the gut and the central nervous system (CNS), with the motor function of the GI tract being controlled at the level of the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells (*Longstreth 2018*).
- Three distinct types of CINV have been defined, including (*Hesketh 2018, Hesketh 2017[a]*):
  - Acute emesis, which most commonly begins within 1 to 2 hours of chemotherapy and usually peaks in the first 4 to 6 hours
  - Delayed emesis, occurring beyond 24 hours after chemotherapy
  - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant n/v during previous cycles of chemotherapy
- 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 2018*).
- 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 2019*).
- Nausea with or without vomiting is common in early pregnancy. 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] 2018, Smith et al 2019*).
- The mechanism of action for the 5-hydroxytryptamine (5-HT3, or serotonin) agents results from the blockade of 5-HT3 receptors in both the gastric area and the chemoreceptor trigger zone in the 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 (NK1) receptor antagonists cross the blood brain barrier and occupy the NK1 receptors in the brain, leading to reduced symptoms of n/v.
- Synthetic delta-9-tetrahydrocannabinol (THC) is the active ingredient in the THC derivative agents, also known as the cannabinoids. Cannabinoid receptors have been discovered in neural tissues, and these receptors may play a role in mediating the antiemetic effects of cannabinoids such as dronabinol and nabilone. These agents, like other cannabinoids, have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood (euphoria, detachment, depression, anxiety) and alterations in reality (distorted perceptions of objects and time and hallucinations).
- The mechanism of action of Diclegis and Bonjesta (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown (*Diclegis and Bonjesta prescribing information*).
- The 5-HT3 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/NK1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.
- The combination product, Akynzeo, contains palonosetron, a 5-HT3 receptor antagonist, and a substance P/NK1 receptor antagonist: netupitant in the oral formulation and fosnetupitant in the injectable formulation. 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 (MA) of controlled studies on outcome of pregnancies exposed to Bendectin reported no increase in the incidence of birth defects (*Smith et al 2019*).
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV. Other agents including anticholinergic agents, antihistamines, glucocorticoids, and dopamine receptor antagonists may also be effective antiemetics; however, they have been excluded from this review.
- Medispan Therapeutic Class: 5-HT3 Receptor Antagonists; Substance P/NK1 Receptor Antagonists; Antiemetics – Miscellaneous; Antiemetic Combinations – Two Ingredient.

**Table 1. Medications Included Within Class Review**

| Drug | Generic Availability |
|---|---|
| Akynzeo (palonosetron/netupitant) capsule | – |
| Akynzeo (palonosetron/fosnetupitant) injection | – |
| Aloxi (palonosetron) IV solution | ✔ |
| Anzemet (dolasetron) tablets¥ | – |
| Bonjesta (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets | – |
| Cesamet (nabilone) capsule | – |
| Cinvanti (aprepitant) IV emulsion | – |
| Diclegis (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets | ✔ § |
| Emend (aprepitant) oral suspension | – |
| Emend (aprepitant) capsule, combination pack | ✔ |
| Emend (fosaprepitant) IV solution | –‖ |
| granisetron injection, tablets | ✔ ‡ |
| Marinol (dronabinol) capsule | ✔ |
| ondansetron injection | ✔ ‡ |
| Sancuso (granisetron) transdermal patch | – |
| Sustol (granisetron) extended-release subcutaneous injection | – |
| Syndros (dronabinol) oral solution | – |
| Varubi (rolapitant) tablet† | – |
| Zofran (ondansetron) oral solution, tablet | ✔ ‡ |
| Zofran ODT (ondansetron) ODT | ✔ ‡ |
| Zuplenz (ondansetron) oral soluble film | – |

Abbrv: IV=intravenous, ODT=orally disintegrating tablet
‡Generic available in at least 1 dosage form and/or strength.
§Actavis received FDA approval for generic Diclegis on August 19, 2016; however, it is not yet marketed.
‖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.
¥ Listed as discontinued on FDA Orange Book; however, per the manufacturer Validus Pharmaceuticals on February 12, 2019, the product is currently on backorder but not discontinued.
†The FDA Web site shows the IV rolapitant product as discontinued. The manufacturer of IV rolapitant suspended further distribution of the product in February 2018 due to reports of anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions associated with its use.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | 5-HT$_3$ Receptor Antagonists | | | | Substance P/NK$_1$ Receptor Antagonists | | | THC Derivatives | | Combination Products | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dolasetron | Granisetron | Ondansetron | Palonosetron | Aprepitant | Fosaprepitant | Rolapitant | Dronabinol | Nabilone | Palonosetron/ netupitant (oral) fosnetupitant (IV) | Doxylamine succinate/ pyridoxine HCl |
| **Anorexia in patients with AIDS** | | | | | | | | | | | |
| Anorexia associated with weight loss in adults with AIDS | | | | | | | | ✔ | | | |
| **CINV** | | | | | | | | | | | |
| N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments | | | | | | | | ✔ | ✔ | | |
| Highly emetogenic cancer chemotherapy (HEC) – 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 HEC including high-dose cisplatin in patients ≥ 6 months of age | | | | | ✔ * (oral suspension) | ✔ * | | | | | |
| Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including HEC in pediatric patients aged 1 month to < 17 years | | | | ✔ | | | | | | | |
| Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in adults | | | | | ✔ * (IV emulsion) | | | | | | |
| Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC | | | | | | | ✔ * | | | | |
| Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC in combination with dexamethasone | | | | | | | | | | ✔ (capsule) | |
| Prevention of acute and delayed n/v associated with initial and repeat courses of HEC in combination with dexamethasone | | | | | | | | | | ✔ ¥ (IV) | |

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| | Dolasetron | Granisetron | Ondansetron | Palonosetron | Aprepitant | Fosaprepitant | Rolapitant | Dronabinol | Nabilone | Palonosetron/ netupitant (oral) fosnetupitant (IV) | Doxylamine succinate/ pyridoxine HCl |
| Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, 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, HEC | | | | | | | ✔ * | | | | |
| Prevention of n/v associated with HEC including cisplatin ≥ 50 mg/m$^2$ | | | ✔ (tablet, ODT, oral solution, oral soluble film) | | | | | | | | |
| 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 initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥ 6 months of age | | | ✔ (injection) | | | | | | | | |
| Moderately emetogenic cancer (MEC) chemotherapy – prevention of n/v associated with initial and repeat courses in adults | | | | ✔ | ✔ * (IV emulsion) | | | | | | |
| Prevention of n/v in patients receiving MEC and/or HEC for up to 5 consecutive days | | ✔ (TD) | | | | | | | | | |
| Prevention of n/v associated with initial and repeat courses of MEC | | | ✔ (tablet, ODT, oral solution, oral soluble film) | | | | | | | | |
| Prevention of n/v associated with MEC, including initial and repeat courses in ages ≥ 2 years | ✔ | | | | | | | | | | |

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| | Dolasetron | Granisetron | Ondansetron | Palonosetron | Aprepitant | Fosaprepitant | Rolapitant | Dronabinol | Nabilone | Palonosetron/ netupitant (oral) fosnetupitant (IV) | Doxylamine succinate/ pyridoxine HCl |
| Prevention of n/v associated with initial and repeat courses of MEC, in patients ≥ 6 months of age | | | | | ✔ (oral suspension) | | | | | | |
| Prevention of acute and delayed n/v associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens. | | ✔ * (ER injection) | | | | | | | | | |
| Prevention of delayed n/v associated with initial and repeat courses of MEC in patients ≥ 6 months of age | | | | | | ✔ * | | | | | |
| Prevention of n/v associated with initial and repeat courses of MEC in patients ≥ 12 years of age | | | | | ✔ * (capsule) | | | | | | |
| **NVP** | | | | | | | | | | | |
| Treatment of NVP in women who do not respond to conservative management | | | | | | | | | | | ✔ |
| **PONV** | | | | | | | | | | | |
| Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been demonstrated; 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, Aloxi injection is recommended even where the incidence of PONV is low | | | | ✔ | | | | | | | |
| Prevention of PONV in adults | | | ✔ (tablet, ODT, oral solution) | | ✔ (capsule) | | | | | | |
| Prevention of PONV; 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, this drug is recommended even where the incidence of PONV is low. | | ✔ (injection) | ✔ (injection†, oral soluble film) | | | | | | | | |

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| | Dolasetron | Granisetron | Ondansetron | Palonosetron | Aprepitant | Fosaprepitant | Rolapitant | Dronabinol | Nabilone | Palonosetron/ netupitant (oral) fosnetupitant (IV) | Doxylamine succinate/ pyridoxine HCl |
| **RINV** | | | | | | | | | | | |
| Prevention of n/v associated with RT, including TBI and fractionated abdominal RT | | ✔ (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) | | | | | | | | |

Abbrv: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, AIDS = acquired immunodeficiency syndrome, ER = extended release, HEC = highly emetogenic cancer chemotherapy, MEC = moderately emetogenic cancer chemotherapy, n/v = nausea/vomiting, NVP = nausea and vomiting of pregnancy, NK1 = neurokinin 1, ODT = orally disintegrating tablet, PONV = postoperative nausea and vomiting, RINV = radiation-induced nausea and vomiting, RT = radiation therapy, TBI = total body irradiation, TD = transdermal patch, THC = delta-9-tetrahydrocannabinol

* When used in combination with other antiemetic agents.

† For patients who do not receive prophylactic ondansetron injection and experience n/v postoperatively, ondansetron injection may be given to prevent further episodes.

¥ Not studied for prevention of n/v associated with anthracycline plus cyclophosphamide chemotherapy.

(*Prescribing information: Akynzeo 2018, Aloxi 2018, Anzemet tablets 2018, Bonjesta 2018, Cesamet 2015, Cinvanti 2018, Diclegis tablets 2018, Emend capsules and oral suspension 2017, Emend for injection 2018, granisetron injection 2018, granisetron tablets 2018, Marinol 2017, ondansetron injection 2018, Sancuso 2017, Sustol 2017, Syndros 2018, Varubi 2018, Zofran tablets ODT oral solution 2017, 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

**Anorexia in patients with AIDS**

- A 2015 MA (N = 6,462; 79 trials) evaluated the efficacy and safety of cannabinoids in various conditions, including appetite stimulation in HIV/AIDS. Most trials were of low to moderate quality and compared cannabinoids to usual care, placebo, or no treatment across trials. Compared with placebo, cannabinoids were associated with a higher proportion of patients demonstrating a complete n/v response (47% vs 20%; odds ratio [OR], 3.82; 95% confidence interval [CI], 1.55 to 9.42; 3 trials), reduction in pain (37% vs 31%; OR, 1.41; 95% CI, 0.99 to 2.00; 8 trials), and a greater average reduction in numerical rating scale pain assessment (on a 0 to 10 point scale; weighted mean difference [WMD], -0.46; 95% CI, -0.80 to -0.11; 6 trials). A total of 4 trials evaluated dronabinol for appetite stimulation in 255 patients with HIV infection or AIDS, key outcomes are outlined below (*Abrams et al 2003, Timpone et al 1997, Whiting et al 2015):*
  - Data from 1 small study (n = 139, of which only 88 were evaluable) demonstrated that a large proportion of patients experienced weight gain of ≥ 2 kg within 6 weeks vs placebo (OR, 2.2; 95% CI, 0.68 to 7.27). An active comparison trial found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.
- A 2013 MA of 7 trials, mostly of poor quality, found similar results as *Whiting et al*. Randomized controlled trials (RCTs) included any cannabis intervention and were of a short duration, ranging from 21 to 84 days. Patients had a mean weight gain in the dronabinol group of 0.1 kg, compared with a weight loss of 0.4 kg in the placebo group (*Lutge et al 2013*).

**CINV**

- For the management of CINV, MAs and head-to-head trials have demonstrated that the cannabinoids, dronabinol and nabilone, are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide. There are no published clinical trials comparing dronabinol to nabilone for CINV. The effectiveness of Syndros (dronabinol) oral solution for its FDA-approved indications was based on studies of dronabinol capsules.
- In a study by *Lane et al,* the combination of dronabinol plus prochlorperazine significantly reduced the mean duration of vomiting per episode compared to either agent administered with placebo (*Lane et al 1991*).
- Dolasetron has been shown to be an effective therapy in the treatment of CINV in comparative studies with palonosetron, 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 ondansetron are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of 1 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*).
- Sancuso (granisetron) patch was non-inferior to orally administered granisetron for CINV (*Boccia et al 2011*).
- 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, Chow et al 2018*).
- The safety and efficacy of Sustol (granisetron) were evaluated in a pivotal Phase 3, double-blind (DB), double-dummy, multicenter (MC), RCT in adults receiving HEC or MEC (*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 HEC and MEC. The FDA-approved dose of granisetron ER 10 mg was non-inferior to palonosetron in preventing delayed CINV after MEC and was not superior in preventing delayed CINV after HEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*).
- All of the 5-HT3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate MAs 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 MA comparing ondansetron to other 5-HT3 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-HT3 receptor antagonists are effective in children who receive emetogenic chemotherapy. Granisetron or palonosetron may be more effective than ondansetron, and the addition of dexamethasone improves vomiting symptoms (*Phillips et al 2016*).

- A randomized, DB, 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, aged 0 to 17 years, receiving MEC or HEC found that palonosetron was non-inferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (*Kovacs et al 2016*). A randomized, DB study in pediatric patients, aged 0 to 18 years, receiving HEC found complete response rates were not significantly different during the acute phase between palonosetron 5 mcg/kg, 10 mcg/kg and ondansetron 150 mcg/kg x 3 doses *(Tan et al 2018).* Palonosetron 10 mcg/kg was superior to ondansetron and palonosetron 5 mcg/kg in the delayed phase. In a randomized, open-label study, palonosetron was found to be non-inferior and cost-effective in comparison to ondansetron for the prevention of acute CINV in children (2 to 18 years of age) with cancer (*Jain et al* 2018).
- A randomized, DB study in patients receiving HEC found that when used as part of combination therapy with dexamethasone and aprepitant, palonosetron IV was not more efficacious than granisetron IV 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 MC, DB, RCT evaluated dexamethasone compared to 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 (ie, no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and aprepitant in the prevention of delayed emesis (*Roila et al 2014*).
- Aprepitant has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT3 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, rolapitant has been shown to be more effective than placebo for the prevention of CINV due to MEC and HEC in clinical trials (*Rapoport et al 2015, Schwartzberg et al 2015*). In combinations with 5-HT3 antagonists and dexamethasone, addition of rolapitant has also been shown to be more effective at preventing CINV over multiple cycles of MEC or HEC, when compared to similar combinations without rolapitant (*Rapoport et al 2016*).
- The fixed-dose combination palonosetron and netupitant + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*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*).
- In a small study, *Meiri et al* reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV, but combination therapy with these 2 agents was not more effective than either agent alone (*Meiri et al 2007*).
- In a large MA (13 dronabinol studies and 16 nabilone studies), treatment with cannabinoids was more effective for complete control of nausea in the first 24 hours of chemotherapy compared to alizapride, chlorpromazine, domperidone, haloperidol, metoclopramide, prochlorperazine, or thiethylperazine (relative risk [RR], 1.38; 95% confidence interval [CI], 1.18 to 1.62; number needed to treat [NNT] = 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT = 8). Of note, cannabinoids were not more effective compared to other agents when the chemotherapy regimen was of very high- or very low-emetogenic risk (*Tramèr et al 2001*).
- In a second MA, authors concluded that with regard to antiemetic efficacy, dronabinol was no more effective compared to placebo (RR, 0.47; 95% CI, 0.19 to 1.16; p = 0.1) but was more effective compared to neuroleptics (RR, 0.67; 95% CI, 0.47 to 0.96; NNT = 3.4). Nabilone was not more effective than neuroleptics (RR, 0.88; 95% CI, 0.72 to 1.08; P = 0.21). With regard to patient preference and tolerability, cannabinoids were preferred over other study agents (RR, 0.33; 95% CI, 0.24 to 0.44; p < 0.00001; NNT = 1.8) (*Machado Rocha et al 2008*).
- In a MA of 23 RCTs (11 dronabinol studies and 12 nabilone studies), compared to placebo, treatment with cannabinoids resulted in a higher chance of reporting complete absence of n/v (RR, 2.9; 95% CI, 1.8 to 4.7; 3 studies); however, patients were more likely to withdraw due to an adverse event compared to placebo (2 trials; RR, 6.9; 95% CI, 1.96 to 24) and compared to prochlorperazine (RR, 3.9; 95% CI, 1.3 to 12; 5 studies). The proportion of patients who reported absence of n/v was not different between cannabinoids and prochlorperazine (*Smith et al 2015*).

**NVP**

- FDA-approvals of Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) were based on 1 DB, 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 n/v. Patients (N = 298) were randomized to 14 days of placebo or 2 tablets daily at bedtime and up to a maximum dose of 4 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*).

**PONV**

- In a MA, palonosetron was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ondansetron (*Xiong et al 2015*).
- A 2016 MA found that when compared to other 5-HT3 antagonists and NK1 antagonists, aprepitant reduces incidence of PONV, and need for rescue medications (*Singh et al 2016*).

**RINV**

- There are very few trials evaluating the prevention of RINV, and trials generally include patients with moderate to high risk RINV. The 5-HT3 receptor antagonists are the only agents in class which have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved.
- One DB, active-comparator trial compared oral ondansetron 8 mg to oral granisetron 2 mg in 34 bone marrow transplant patients receiving TBI, which is associated with high emetogenic risks. The study was only powered to demonstrate a difference between each active treatment groups and historical controls. In the intention-to-treat population, significantly more patients given granisetron (33.3%) or ondansetron (26.7%) had zero emetic episodes over 4 days, the primary efficacy end point, than those within the historical control group (0%) (p < 0.01) (*Spitzer et al 2000).*
- In a MA of 9 trials, fewer patients had residual emesis with 5-HT3 receptor antagonists compared with placebo (40% vs 57%; RR, 0.7; 95% CI, 0.57 to 0.86), and fewer required rescue medication (6.5% vs 36%; RR, 0.18; 95% CI, 0.05 to 0.60). Despite treatment, most patients did develop RT-induced nausea (70% vs 83%; RR 0.84; 95% CI, 0.73 to 0.96) (*Salvo et al 2012*).

## CLINICAL GUIDELINES

- The 5-HT3 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. Treatment of CINV, RINV or PONV generally involves the use of multiple agents that affect different receptor types (*American Gastroentrological Association [AGA], 2001, Herrstedt et al 2017, Hesketh et al 2017[b], Gan et al 2014, Gupta et al 2016, Roila et al 2010).*
- 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 2017 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (*Hesketh et al 2017[b]*):
  - For the prevention of n/v induced by HEC, a 4 drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine is recommended as first-line therapy.
  - For MEC, other than carboplatin area under the curve (AUC) ≥ 4 mg/mL/min, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For MEC that includes carboplatin AUC ≥ 4 mg/mL/min, a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended.

- For children receiving HEC or MEC, a 3-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant is recommended. A 2-drug regimen of a 5-HT3 receptor antagonist and dexamethasone can be used if aprepitant cannot be given; palonosetron and aprepitant can be used if dexamethasone cannot be given.
- Cannabinoids (eg, nabilone, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk. These agents can be used in conjunction with standard regimens for patients who continue to have symptoms despite optimal prophylaxis (including use of olanzapine).

- The 2019 National Comprehensive Cancer Network (NCCN) antiemesis guideline recommends the following regimens for prevention of CINV depending on emetic risk (order does not imply preference) *(NCCN 2019):*
  - For high emetic risk IV chemotherapy on day 1: 1) NK-1receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) olanzapine, NK-1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone. Additional agents depending on the regimen are used on days 2, 3, and 4.
  - For moderate emetic risk IV chemotherapy on day 1: 1) 5-HT3 receptor antagonist plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) NK-1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone. Additional agents depending on the regimen are used on days 2 and 3.
  - For high to moderate emetic risk oral chemotherapy: 5-HT3 receptor antagonist started before chemotherapy and continued daily.
- The NCCN guideline recommends granisetron ± dexamethasone or ondansetron ± dexamethasone for pretreatment for RINV in patients receiving radiation therapy (upper abdomen/localized site) or total body irradiation *(NCCN 2019).*
- The 2018 ACOG Practice Bulletin for NVP recommends the following algorithm (*ACOG 2018*):
  - First-line non-pharmacologic options: Change the prenatal vitamin to 1 that contains only folic acid, ginger capsules, and P6 acupressure with wrist bands.
  - If symptoms persist, escalate to first-line pharmacologic interventions: pyridoxine (vitamin B6) monotherapy or pydridoxine in combination with doxylamine in various doses.
  - If symptoms persist, oral dimenhydrinate, oral diphenhydramine, rectal prochlorperazine, or oral/rectal promethazine may be added.
  - If there is no dehydration and symptoms persist, oral/intramuscular (IM) metoclopramide, oral ondansetron, oral/rectal/IM promethazine, or IM trimethobenzamide may be added.
  - If there is dehydration, patients should receive IV fluid replacement. If symptoms persist, IV dimenhydrinate, IV metoclopramide, IV ondansetron, or IV promethazine may be added.
    - If symptoms continue to persist, IM/IV chlorpromazine or oral/IV methylprednisolone may be added.

## SAFETY SUMMARY

- The 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated. Ondansetron is also contraindicated with apomorphine.
- The 5-HT3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for dolasetron regarding the risk of arrhythmias. Ondansetron and granisetron have QTc prolongation as a general precaution. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Ondansetron and granisetron may mask progressive ileus or gastric distention following abdominal surgery or in patients with CINV.
- Aprepitant and fosaprepitant are moderate inhibitors of CYP3A4 and aprepitant is an inducer of CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted with these agents. Aprepitant, fosaprepitant, and rolapitant are contraindicated taking CYP substrates of the respective enzymes that have a narrow therapeutic index, pimozide and thioridazine. Increased plasma concentrations may result in QT prolongation and torsades de pointes.
- Fosaprepitant, aprepitant, and rolapitant can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate aprepitant, fosaprepitant, or rolapitant IV in patients who experience hypersensitivity symptoms with first-time use. Infusion site reactions have been reported with fosaprepitant IV; avoid infusion into small veins or through a butterfly catheter.
- Dronabinol and nabilone have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood and alterations in reality (distorted perceptions of objects and time and hallucinations).

- Dronabinol and nabilone are contraindicated in individuals who are allergic to cannabinoids. Syndros (dronabinol oral solution) is contraindicated in patients with hypersensitivity to alcohol and in patients who have received products containing disulfiram or metronidazole within 14 days. Syndros contains dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). Disulfiram- and metronidazole-containing products should not be administered within 7 days of completing Syndros treatment.
- Consider risks and benefits of using dronabinol in patients with a history of seizures. Patients with cardiac disorders may experience cardiac effects such as hypotension, hypertension, syncope, or tachycardia with cannabinoids.
- Dronabinol and nabilone may exacerbate or unmask symptoms of mania, depression, or schizophrenia.
- Common adverse events with cannabinoids were dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance.
- Syndros and Marinol both contain the same active ingredient, dronabinol, and the safety of Syndros oral solution was based on studies using dronabinol capsules. Additional warnings and precautions include:
  - Avoid dronabinol in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of dronabinol cannot be avoided.
  - Reduce the dose or discontinue if signs and symptoms of cognitive impairment occur.
  - Consider a dose reduction or discontinue in patients who develop worsening nausea, vomiting, or abdominal pain while taking dronabinol.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAOIs), as they intensify and prolong the adverse effects of the agent. 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, are not recommended (unless cleared to do so by a health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties. It 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. Additionally, false positive urine screening tests for methadone, opiates, and phencyclidine (PCP) have been reported with doxylamine/pyridoxine use.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| **5-HT$_3$ Receptor Antagonists** | | | | |
| Dolasetron | Tablet | Oral | Take within 1 hour before chemotherapy. | Indicated in both pediatric (age 2 to 16 years based on adult PK data) and adults.<br><br>ECG monitoring recommended in patients with renal impairment and the elderly. |
| Granisetron | Tablet, injection, injection ER, TD patch | Oral, IV, SC, TD | Take orally within 1 hour before chemotherapy or radiation, or twice daily.<br><br>Administer patch a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion<br><br>Administer IV or SC within 30 minutes before chemotherapy or administer IV right before induction | Injection approved for CINV in children 2 to 16 years. Tablet, injection ER, and TD patch have not studied in pediatrics.<br><br>Do not use injection ER in severe renal impairment and adjust frequency in moderate renal impairment.<br><br>Apply patch to upper outer arm. The patch may be worn for up to 7 days |

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| | | | of anesthesia or immediately before reversal of anesthesia. Do not administer SC injection ER more frequently than once a week. | depending on the duration of the chemotherapy regimen. |
| Ondansetron | Tablet, oral solution, ODT, oral soluble film, IV solution, injection | Oral, lingual, IV, IM | Oral administrations vary: (1) Give within 30 minutes before HEC or; (2) given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before induction of anesthesia or; (6) for pediatric patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy.<br><br>IV administrations vary: (1) administer IV over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given 4 and 8 hours after the first dose or; (2) administer IV over 2 to 5 minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within 2 hours after surgery or; (3) for pediatric patients administer IV over 2 to 5 min immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences | Do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥10). There is no experience beyond first-day administration in these patients.<br><br>Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month. |

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| | | | nausea and/or vomiting occurring shortly after surgery.<br><br>Administer IM as a single dose. | |
| Palonosetron | IV solution | IV | IV administrations vary: (1) administer IV over 30 seconds, approximately 30 minutes before the start of chemotherapy or; (2) administer IV over 10 seconds immediately before the induction of anesthesia or; (3) for pediatric patients, administer IV over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy | IV solution approved for prevention of CINV in pediatric patients aged ≥ 1 month. |
| **Substance P/$NK_1$ Receptor Antagonists** | | | | |
| Aprepitant | Capsule, combination pack, oral suspension, IV emulsion | Oral, IV | Take orally within 1 hour before chemotherapy and once daily for 2 additional days or; 3 hours prior to induction of anesthesia.<br><br>Administer IV over 30 minutes beginning 30 minutes before chemotherapy (for the 3-day regimen, continue capsules on day 2 and 3). | Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist.<br><br>Oral suspension approved for prevention of CINV in pediatric patients aged 6 months to < 12 years.<br><br>Give with or without food.<br><br>Use with caution in severe hepatic impairment. |
| Fosaprepitant | IV solution | IV | Adults: Administer IV over 20 to 30 minutes before chemotherapy.<br><br>Administer IV over 30 minutes (12 to 17 years) or 60 minutes (6 months to <12 years) (for the 3-day regimen, continue capsules or oral suspension on days 2 and 3).<br><br>Complete infusion approximately 30 minutes prior to chemotherapy | Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist.<br><br>Use with caution in severe hepatic impairment. |
| Rolapitant | Tablet | Oral | Administer orally within 2 hours prior to chemotherapy. | Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist.<br><br>Avoid use in severe hepatic impairment; if use cannot be avoided, monitor for adverse events. |
| **THC derivatives** | | | | |

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| Dronabinol | Capsule, oral solution | Oral | Take orally 1 to 3 hours before chemotherapy and subsequent doses every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day or; take orally twice daily, one hour prior to lunch and dinner. | If adverse effects occur and do not resolve in 1 to 3 days with continued use, consider dose reductions.<br><br>In elderly, consider decreasing the initial dose to reduce risk of CNS adverse reactions.<br><br>Always use calibrated oral dosing syringe for administration; if the prescribed dose is > 5 mg, it must be divided in multiple doses.<br><br>Take with 6 to 8 ounces of water (oral solution). |
| Nabilone | Capsule | Oral | Take orally twice daily; initial dose is given 1 to 3 hours before chemotherapy and subsequent doses 2 to 3 times daily. | |
| **Combination products** | | | | |
| Palonosetron/ netupitant<br><br>Palonosteron/ fosnetupitent | Capsule<br><br>Powder for injection | Oral<br><br>IV | Oral administration: Take orally within 1 hour before chemotherapy<br><br>IV administration: Infuse over 30 minutes starting 30 minutes before chemotherapy. | Given as part of a regimen that includes a corticosteroid.<br><br>Do not use in severe renal or hepatic impairment. |
| Doxylamine succinate/ pyridoxine HCl | Tablet ER, tablet DR | Oral | Take orally at bedtime. Titrate dose to twice daily (for the 20/20 mg tablet ER) or 3 times daily (for the 10/10 mg tablet DR). | Bonjesta is available in 20/20 mg tablets ER and Diclegis is available in 10/10 mg tablets DR.<br><br>Should be taken on an empty stomach with a glass of water. |

Abbrv: DR = delayed release, ER = extended release, IV = intravenous, ODT = orally disintegrating tablet, PK = pharmacokinetic, SC = subcutaneously, TD = transdermal
See the current prescribing information for full details.

## CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. There are several classes of antiemetic drugs that may influence the neurotransmitter receptors involved in the pathway associated with n/v (*Longstreth 2018*)
- Choice of agents generally depends upon the relative emetogenic potential of the influencing agent, condition, or procedure, including chemotherapy or radiation therapy. Various formulations may be prescribed based on age of the patient, indication, and persistence of symptoms (*AGA 2001, ACOG 2018, Hesketh et al 2017[b], Longstreth 2018, Roila et al 2010; NCCN 2019*).
- Guideline recommendations vary according to indication. The 2017 ASCO antiemetic guidelines recommend a 4-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine as first-line therapy for the prevention of CINV due to HEC. For MEC, a 2-drug combination of a 5-HT3 receptor antagonist plus dexamethasone is recommended for regimens other than carboplatin area AUC ≥ 4 mg/mL/min or a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone for patients treated with a regimen that includes carboplatin AUC ≥ 4 mg/mL/min (*Hesketh et al 2017[b]*). 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 2018*).

- The 5-HT3 antagonists are the cornerstone of therapy for acute emesis with MEC to HEC agents in the management of CINV, in addition to RINV and PONV. These agents include dolasetron, granisetron, ondansetron, and palonosetron. Ondansetron is the most well studied medication; however, trials haven't demonstrated a clear treatment leader between dolasetron, granisetron, and ondansetron. Palonosetron has a longer half-life and a higher receptor binding affinity than the other 5-HT3 receptor antagonists. Single-dose therapy with palonosetron is reported to be more effective than other medications in the class, particularly at preventing delayed emesis. There are very few trials evaluating the prevention of RINV. The 5-HT3 receptor antagonists are the only agents in this class review with demonstrated efficacy and, of these, only ondansetron and granisetron are FDA-approved. Oral formulations appear to have comparable efficacy to IV formulations in CINV. The 5-HT3 receptor antagonists are generally well tolerated, with mild headache the most frequent adverse event. Cardiac abnormalities ranging from ECG interval changes to torsade de pointes or QTc prolongation have been reported with dolasetron, granisetron, and ondansetron. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists (*Aapro et al 2005, AGA, 2001, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gan et al 2014, Gralla et al 2003, Gupta et al 2016, Herrstedt et al 2017, Hesketh et al 2017[b], Kaushal et al 2010, Kovacs et al 2016, Likun et al 2011, Longstreth 2018, Roila et al 2010, Salvo et al 2012, Simino et al 2016, Spitzer et al 2000, Suzuki et al 2016*).
  - All 5-HT3 antagonist formulations are available generically with the exception of Anzemet (dolasetron) tablets, Sancuso (granisetron) transdermal patch, Sustol (granisetron) extended-release injection, and Zuplenz (ondansetron) oral soluble film.
- The substance P/NK1 receptor antagonists are prescribed for both acute and delayed CINV, which is an advantage over first-generation serotonin antagonists that are generally effective for acute emesis only. These include aprepitant, fosaprepitant, and rolapitant. The substance P/NK1 receptor antagonists are most effective when used in combination with other agents, typically a 5-HT3 antagonist, a glucocorticoid, ± olanzapine, for patients receiving HEC. One MA concluded aprepitant reduces incidence of PONV and need for rescue medications compared to other 5-HT3 and NK1 antagonists. Aprepitant and fosaprepitant are moderate inhibitors of the CYP3A4 pathway and rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have also been reported in patients receiving IV formulations, some requiring hospitalization (*AGA 2001, Gralla et al 2005, Grunberg et al 2011, Hesketh et al 2017[b], Herrington et al 2008, Herrstedt et al 2005, Longstreth 2018, Rapoport et al 2010, Roila et al 2010, Singh et al 2016, Warr et al 2005, Yeo et al 2009)*.
  - The only substance P/NK1 receptor antagonist formulations available generically are aprepitant capsules and combination pack.
- The THC derivatives, also referred to as the cannabinoids, have been prescribed for CINV and also have properties that may contribute to weight gain. The agents include nabilone and dronabinol. Dronabinol is also FDA-approved for anorexia associated with weight loss in adults with AIDS. In terms of CINV, these agents have a modest antiemetic activity and a relatively unfavorable adverse event profile. Side effects include vertigo, xerostomia, hypotension, and dysphoria, particularly in elderly patients. Trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine; however, no head-to-head trials have been conducted. The cannabinoids have little clinical utility. Due to the availability of other agents that are more effective and better tolerated, dronabinol and nabilone are recommended for later line therapy *(Hesketh et al 2017[b], Lane et al 1991, Longstreth 2018, Meiri et al 2007, Machado Rocha et al 2008, Tramer et al 2001)*.
  - Only Marinol (dronabinol) oral capsules are available generically.
- Combination products include Diclegis and Bonjesta (doxylamine succinate/pyridoxine) and Akynzeo (palonosetron/netupitant and palonosetron/fosnetupitant). Doxylamine succinate/pyridoxine is the only agent in this class FDA-approved for NVP and is guideline-recommended as a first-line pharmacologic therapy. Diclegis and Bonjesta vary by fixed dose strengths; however, each individual component is available over-the-counter (*ACOG 2018)*. The fixed-dose combination Akynzeo (palonosetron/netupitant) with dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*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*). Netupitant is also a moderate inhibitor of the CYP3A4 pathway and clinicians should be aware of potential drug interactions.

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