Therapeutic Class Overview
Antiemetics - Delta-9-Tetrahydrocannabinol (THC) Derivatives

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant vomiting, which is the forceful expulsion of gastric contents, dyspepsia, and other gastrointestinal (GI) symptoms (Longstreth, 2016).
- 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, 2016).
- An undesired outcome of surgery, opiate therapy, radiation, and other external noxious stimuli, chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (N/V) (Hesketh, 2017[a]; Hesketh, 2017[b]). Additional causes of N/V include pregnancy, vestibular neuritis, gastroenteritis, gastroparesis, GI obstruction, and rumination syndrome (Longstreth, 2016).
- Three distinct types of CINV have been defined, including (Hesketh, 2017[a]; Hesketh, 2017[b]):
    - Acute emesis, which most commonly begins within one to two hours of chemotherapy and usually peaks in the first four to six hours;
    - Delayed emesis, occurring beyond 24 hours after chemotherapy; and
    - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant N/V during previous cycles of chemotherapy.
- The precise mechanism by which chemotherapy induces emesis remains unclear; however, proposed theories include chemotherapeutic agents and their metabolites interacting directly and indirectly with receptors in the limbic forebrain (e.g., amygdala); intestinal cell wall damage caused by chemotherapy which results in 5-hydroxytryptamine (5-HT) activating the emetic cascade; as well as the release of substance P from sensory neurons after chemotherapy administration (Hesketh, 2017[a]).
- Physiologic pathways involved in the treatment of N/V primarily involve dopamine and serotonin ($5\text{-}HT_3$). Other receptors, which have a lesser role, include muscarinic, opiate, histamine H_1, cannabinoid, and neurokinin 1 (NK1) (Andrews et al, 1998; Lynch, 2005).
- Chemotherapy agents, which often cause N/V as adverse effects, are categorized based upon their emetogenicity.
    - High emetogenicity is associated with a >90% risk of emesis.
    - Moderate emetogenicity is associated with a >30 to 90% risk of emesis.
    - Low emetogenicity is associated with a 10 to 30% risk of emesis.
    - Minimal emetogenicity is associated with a <10% risk of emesis (Hesketh, 2017[a]; Hesketh, 2017[b]).
- 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).
- Dronabinol and nabilone are Food and Drug Administration (FDA)-approved for the treatment of CINV in patients failing to respond to conventional antiemetic treatments.
- The 2016 American Society of Clinical Oncology (ASCO) antiemetic guidelines do not designate cannabinoids (e.g., nabilone, dronabinol) as appropriate first-line antiemetics for patients receiving chemotherapy of high to low emetic risk (Hesketh et al, 2016).
- Medispan Class: Antiemetics – Miscellaneous
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
CESAMET® (nabilone)	Meda Pharms	12/26/1985	–
MARINOL® (dronabinol)	Abbvie	05/31/1985	✔
SYNDROS™*(dronabinol)	Insys	7/1/2016	–

*SYNDROS has not yet been marketed
(DRUGS@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	CESAMET (nabilone)	MARINOL (dronabinol)	SYNDROS (dronabinol)
Anorexia associated with weight loss in patients with AIDS.		✔	✔
N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.	✔	✔	✔

(Prescribing information: MARINOL, 2016; CESAMET, 2013; SYNDROS, 2016)

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

CLINICAL EFFICACY SUMMARY

- For the management of CINV, meta-analyses and head-to-head trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide.
- 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).
- 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 two agents was not more effective than either agent alone (Meiri et al, 2007).
- In a large meta-analysis (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 meta-analysis, 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).
- A third meta-analysis evaluated the efficacy and safety of cannabinoids in various conditions, including CINV (Whiting et al, 2015). In these indications, compared to placebo, cannabinoids were associated with a higher proportion of patients with a complete N/V response (47% vs 20%; odds ratio [OR], 3.82; 95% CI, 1.55 to 9.42). However, these results reflect the effects of cannabinoids that are not FDA-approved, which were included in the analysis.
- In a meta-analysis of 23 randomized controlled trials (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 (3 studies; RR, 2.9; 95% CI, 1.8 to 4.7); 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 (5 studies; RR, 3.9; 95% CI, 1.3 to 12). The proportion of patients who reported absence of N/V was not different between cannabinoids and prochlorperazine (Smith et al, 2015).
- 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.
- The 2016 ASCO antiemetic guidelines recommend the following for CINV (Hesketh et al, 2016):
    - For the prevention of N/V induced by highly emetogenic chemotherapy agents, a three drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone is recommended as first-line therapy.
    - For moderately emetogenic agents, a two-drug combination of ALOXI (palonosetron) and dexamethasone is recommended.
    - For children receiving highly or moderately emetogenic agents, a 5-HT_3 receptor antagonist plus a corticosteroid is recommended.
    - Cannabinoids (e.g., nabilone, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk.

SAFETY SUMMARY

- Dronabinol and nabilone are synthetic, orally active cannabinoids, which have complex effects on the central nervous system, including central sympathomimetic activity.
- These agents, like other cannabinoids, 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 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 seven days of completing SYNDROS treatment.
- In both placebo and active controlled trials, greater than 10% of patients experienced dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance with either cannabinoid.
- 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.
- SYNDROS and MARINOL both contain the same active ingredient, dronabinol, and the safety of SYNDROS oral solution was based on studies using dronabinol capsules. The SYNDROS prescribing information contains updated warnings and precautions, including:
    - Avoid SYNDROS in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of SYNDROS 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 SYNDROS.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Dose	Other Dosing Considerations
MARINOL (dronabinol)	Capsule: 2.5 mg 5 mg 10 mg	**ADULT** <u>Treatment of chemotherapy-induced nausea and vomiting:</u> Capsule: initial, 5 mg/m^2 given one to three hours prior to the administration of chemotherapy; maintenance, 5 mg/m^2 every two to four hours after chemotherapy for a total of four to six doses/day; maximum, the dose may be titrated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose in the absence of significant adverse events. <u>Treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome:</u>	Capsules are not recommended for AIDS-related anorexia in pediatric patients, because safety and efficacy have not been established.

Drug	Dosage Form: Strength	Dose	Other Dosing Considerations
		Capsule, initial, 2.5 mg orally twice daily, prior to lunch and dinner; if adverse effects occur and do not resolve in one to three days with continued use, reduce dose to 2.5 mg per day before dinner or at bedtime; maximum, 20 mg per day if clinically indicated and absence of significant adverse events. **PEDIATRIC** <u>Treatment of chemotherapy-induced nausea and vomiting:</u> Capsule: initial, 5 mg/m^2 administered one to three hours prior to the administration of chemotherapy; maintenance, 5 mg/m^2 every two to four hours after chemotherapy for a total of four to six doses/day; maximum, the dose may be titrated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose in the absence of significant adverse events.	
SYNDROS (dronabinol)	Oral solution: 5 mg/mL	**ADULT** <u>Treatment of chemotherapy-induced nausea and vomiting:</u> Oral solution: initial, 4.2 mg/m^2 one to three hours prior to chemotherapy then every two to four hours after chemotherapy for a total of four to six doses per day; titrate dose to clinical response as tolerated in increments of 2.1 mg/m^2; maximum, 12.6 mg/m^2 per dose for four to six doses per day; consider decreasing dose to 2.1 mg once daily one to three hours prior to chemotherapy to reduce risk of CNS adverse reactions. In elderly, consider initiating dose at 2.1 mg/m^2 once daily one to three hours prior to chemotherapy. <u>Treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome:</u> Oral solution: initial, 2.1 mg twice daily to begin one hour before lunch and dinner; dosage may be increased gradually to 2.1 mg one hour before lunch and 4.2 mg one hour before dinner; the dose may be further increased to 4.2 mg one hour before lunch and dinner; maximum, 8.4 mg twice daily; reduce dose to 2.1 mg once daily one hour prior to dinner or prior to bedtime if CNS adverse reactions are severe or persistent. In elderly, consider initiating dose at 2.1 mg once daily one hour before dinner or at bedtime.	Always use calibrated oral dosing syringe for administration; the oral syringe holds a maximum of 5 mg; if the prescribed dose is greater than 5 mg, it must be divided in multiple doses. Take with 6 to 8 ounces of water. For CINV: round initial dose to nearest 0.1 mg increment; the dose may need to be rounded to the nearest 0.1 mL increment to correspond with a calibrated oral dosing syringe. Administer first dose on an empty stomach at least 30 minutes before eating. Subsequent doses can be taken without regard to meals, but timing of dose in regard to meal times should be kept consistent.

Drug	Dosage Form: Strength	Dose	Other Dosing Considerations
CESAMET (nabilone)	Capsule: 1 mg	**ADULT** Treatment of chemotherapy-induced nausea and vomiting: Capsule: initial, 1 to 2 mg twice daily to begin one to three hours prior to the administration of chemotherapy; dose of 1 or 2 mg the night before chemotherapy may be useful; may be administered two or three times daily during the entire course of each cycle and, if needed, for 48 hours after the last dose of each cycle; maximum, 2 mg three times a day.	Safety and efficacy in children <18 years of age have not been established.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
CESAMET (nabilone)	Safety and efficacy in elderly patients have not been established.	Safety and efficacy in children <18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk. Because many drugs including some cannabinoids are excreted in breast milk; use is not recommended in nursing mothers.
MARINOL (dronabinol)	Caution advised in the elderly as they may be more sensitive to neurological, psychoactive and hypotensive effects.	Pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Not recommended for AIDS-related anorexia as it has not been studied in this population.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy Category C Dronabinol is excreted in breast milk; use is not recommended in nursing mothers.
SYNDROS (dronabinol)	Caution advised in the elderly as they may be more sensitive to neurological, psychoactive and hypotensive effects; elderly patients with dementia are at an increased risk for falls.	Safety and efficacy in pediatric patients have not been established. Avoid use in preterm neonates in the immediate postnatal period due to possible propylene glycol-associated toxicities.	No dosage adjustment required.	No dosage adjustment required.	Unclassified† Women infected with HIV are advised not to breastfeed; women with CINV are advised not to breastfeed during SYNDROS treatment or for at least 9 days after the last dose.

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

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

CONCLUSION

- Physiologic pathways involved in the treatment of nausea and vomiting primarily involve dopamine and serotonin (5-HT_3). Other receptors, which have a lesser role, include muscarinic, opiate, histamine H_1, cannabinoid and neurokinin 1.
- Treatment of chemotherapy-induced nausea and vomiting (CINV) generally involves the use of multiple agents that affect different receptor types, such as a dopamine antagonist, a steroid, and a 5-HT_3 receptor antagonist (Basch et al, 2011).
- The choice of antiemetic therapy is generally dependent upon the relative emetogenic potential of the chemotherapy regimen. If one antiemetic regimen is ineffective, it is appropriate to use or add a different agent. General practice guidelines state, if breakthrough emesis or nausea occurs, the addition of an agent with a different mechanism of action is recommended. The American Society of Clinical Oncology (ASCO) guidelines for antiemetics in oncology do not consider cannabinoids (e.g., nabilone, dronabinol) appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk (Hesketh et al, 2016).
- Dronabinol and nabilone are Food and Drug Administration (FDA)-approved for the treatment of CINV in patients failing to respond to conventional antiemetic treatments. Meta-analyses and placebo-controlled trials demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine (Lane et al, 1991; Meiri et al, 2007; Machado Rocha et al, 2008; Tramer et al, 2001).
- Due to the availability of other agents that are more effective and better tolerated compared to the cannabinoids, dronabinol and nabilone are not considered first-line agents. Both of these agents have a high abuse potential and are regulated under the Controlled Substances Act.
- There are no head-to-head studies comparing dronabinol to nabilone for their FDA-approved indications. Dronabinol capsules (MARINOL) are available in a generic formulation while dronabinol oral solution (SYNDROS) and nabilone (CESAMET) are only available as branded agents.

Table 5. Advantages and Disadvantages of Delta-9-Tetrahydrocannabinol (THC) Derivatives

Drug	Advantages	Disadvantages
CESAMET (nabilone)	• Dosed twice daily	• CESAMET is a schedule II controlled substance
MARINOL (dronabinol)	• Generic formulation available. • Also indicated for anorexia associated with weight loss in adult patients with AIDS • Indicated in adult and pediatric populations for CINV	• MARINOL is a schedule III controlled substance • Requires refrigeration • Dosed three to four times daily
SYNDROS (dronabinol)	• Oral solution • Also indicated for anorexia associated with weight loss in adult patients with AIDS	• SYNDROS is a schedule II controlled substance • SYNDROS contains 50% (w/w) dehydrated alcohol and 5.5% (w/w) propylene glycol

(Insys Therapeutics)

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