

# BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults

***Protocol Code***

SCNAUSEA

***Tumour group***

SUPPORTIVE CARE

***Physician Contact***

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## ELIGIBILITY

- Adults receiving chemotherapy.
- Drug acquisition: Antiemetics are considered supportive treatment. These agents are not BC Cancer benefit drugs and are not covered by any BC Cancer program. Patients being treated with these agents should have prescriptions filled at a community pharmacy and must arrange their own payment for the drugs.

## EXCLUSION CRITERIA

- Pediatric patients.
- Radiation-induced nausea and vomiting.

## APPROACH TO TREATMENT

- The goal is NO nausea or vomiting.<sup>1-3</sup>
- It is far easier to prevent nausea and vomiting than to treat it.<sup>1,2</sup>
- Anticipatory nausea and vomiting is a conditioned response, and can only happen after a negative past experience.<sup>1,2</sup>
- Ensure optimal antiemetic therapy for every cycle of chemotherapy.
- Use of guidelines: This is a general reference based upon best available evidence and is not intended to replace the clinical judgment of individual practitioners caring for individual patients.

## PROPHYLACTIC ANTIEMETIC REGIMENS FOR IV AND COMBINED IV / ORAL CHEMOTHERAPY

- For multiple days of chemotherapy, repeat antiemetics *before each* treatment (*Exception: netupitant-palonosetron is dosed on day 1 only*).
- See comment below table for ORAL chemotherapy regimens.
- For prophylaxis after prior treatment failures, refer to Figure 1.

EMETOGENICITY	PRE-CHEMOTHERAPY <sup>o</sup>	POST-CHEMOTHERAPY
High (HEC)*	dexamethasone <sup>s</sup> 8 to 12 mg PO <sup>1-3</sup> <b>PLUS NK<sub>1</sub> and 5-HT<sub>3</sub> ANTAGONIST</b>	dexamethasone <sup>s</sup> 4 mg PO evening of chemo, <sup>3</sup> then BID x 2 to 4 days <sup>2,3</sup>
	<ul style="list-style-type: none"> <li>• netupitant-palonosetron 300 mg-0.5 mg<sup>†</sup> PO<sup>18</sup></li> </ul> <p style="text-align: center;"><b>OR</b></p> <ul style="list-style-type: none"> <li>• aprepitant<sup>†</sup> 125 mg PO<sup>7-9</sup></li> <li>• <b>PLUS one 5-HT<sub>3</sub> antagonist<sup>  </sup>:</b> <ul style="list-style-type: none"> <li>○ ondansetron 8 mg PO<sup>3</sup></li> <li>○ granisetron 1 mg PO<sup>17,19</sup></li> <li>○ palonosetron 0.5 mg PO<sup>17,19</sup></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• No post-chemotherapy netupitant-palonosetron</li> </ul> <p style="text-align: center;"><b>OR</b></p> <ul style="list-style-type: none"> <li>• aprepitant<sup>#</sup> 80 mg PO daily on days 2 and 3, <b>IF</b> aprepitant used on day 1<sup>2,8,9</sup></li> </ul> <p><b>+/- ONE ANTIEMETIC “AS-NEEDED” (if not using olanzapine):</b></p> <ul style="list-style-type: none"> <li>• prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days<sup>3,18</sup> <b>OR</b></li> <li>• metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days<sup>3,4,18,19</sup></li> </ul>
	+/- olanzapine <sup>¶</sup> 2.5 to 10 mg PO <sup>15,18,30,31</sup>	+/- olanzapine <sup>¶</sup> 2.5 to 10 mg PO daily on days 2, 3 and 4 (if olanzapine used on day 1 <sup>15,18,30,31</sup> ; do NOT use with prochlorperazine or metoclopramide)
Moderate (MEC)*	dexamethasone <sup>s</sup> 8 to 12 mg PO <sup>3,18</sup> <b>PLUS ONE 5-HT<sub>3</sub> ANTAGONIST:</b>	dexamethasone <sup>s</sup> 4 mg PO evening of chemo, <sup>3</sup> then PO BID x 2 to 3 days <sup>2,3</sup>
	<ul style="list-style-type: none"> <li>• ondansetron 8 mg PO<sup>3</sup></li> <li>• granisetron 1 mg PO<sup>17,19</sup></li> <li>• palonosetron 0.5 mg PO<sup>17,19</sup></li> </ul>	<p><b>+/- ONE ANTIEMETIC “AS-NEEDED” (if not using olanzapine):</b></p> <ul style="list-style-type: none"> <li>• prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days<sup>3,18</sup> <b>OR</b></li> <li>• metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days<sup>3,4,18,19</sup></li> </ul>
	+/- olanzapine <sup>¶</sup> 2.5 to 10 mg PO <sup>15,16,18,30,31</sup>	+/- olanzapine <sup>¶</sup> 2.5 to 10 mg PO daily on days 2 and 3 <sup>15,16,18,30,31</sup> (if olanzapine used on day 1 <sup>15</sup> ; do NOT use with prochlorperazine or metoclopramide)
Low	<ul style="list-style-type: none"> <li>• dexamethasone<sup>s</sup> 4 to 12 mg PO<sup>1,2</sup> <b>OR</b></li> <li>• prochlorperazine 10 mg PO<sup>18</sup> <b>OR</b></li> <li>• metoclopramide 10 to 20 mg PO<sup>3,4,18</sup> <b>OR</b></li> <li>• ondansetron 8 mg PO<sup>17-19</sup> <b>OR</b></li> <li>• granisetron 1mg PO<sup>17-19</sup> <b>OR</b></li> <li>• no prophylaxis<sup>19</sup></li> </ul>	<ul style="list-style-type: none"> <li>• dexamethasone 4 mg BID PRN for up to 2 to 3 days<sup>1-3</sup> <b>OR</b></li> <li>• prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days<sup>3,18</sup> <b>OR</b></li> <li>• metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days<sup>3,4,18,19</sup> <b>OR</b></li> <li>• no prophylaxis<sup>3,18,19</sup></li> </ul>
Minimal (Rare)	Prophylactic treatment not normally required <sup>18,19</sup>	<ul style="list-style-type: none"> <li>• prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days<sup>3,18</sup> <b>OR</b></li> <li>• metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days<sup>3,4,18,19</sup> <b>OR</b></li> <li>• no prophylaxis<sup>3,18,19</sup></li> </ul>

°Pre-chemotherapy is interpreted as 30 to 60 minutes prior to the start of chemotherapy

\*Highly emetogenic chemotherapy (HEC), Moderately emetogenic chemotherapy (MEC); MEC replaces high-moderate and low-moderate in previous versions

§Dexamethasone doses may be individualized. When netupitant-palonosetron is used with anthracycline and cyclophosphamide (AC) based protocols, omission of day 2 to 4 dexamethasone doses is recommended. In general, lower dexamethasone doses and/or shorter durations may be considered for patients on non-CISplatin regimens. Steroids are not recommended as antiemetics for immunotherapies<sup>18,29</sup>

‡Netupitant-palonosetron 300 mg-0.5 mg capsules are a fixed dose, combination product given on day 1 only. Aprepitant is the NK<sub>1</sub> antagonist of choice for docetaxel containing regimens; pharmacokinetic studies demonstrate a 35% increase in docetaxel AUC when co-administered with netupitant.<sup>29</sup> Netupitant-palonosetron is likely safe to use in patients with soy/peanut allergies; however, a very low potential for allergic reaction does exist as trace amounts of soya lecithin may be present.<sup>30</sup>

†For inpatients unable to swallow:

- Consider replacing pre-chemotherapy aprepitant with fosaprepitant IV 150 mg
- Post-chemotherapy fosaprepitant NOT needed,<sup>2,9,10</sup> dose of 5-HT<sub>3</sub> antagonist and dexamethasone remain the same (fosaprepitant 150 mg confers comparable serum level to aprepitant 125 mg<sup>11</sup> which seems sufficient to cover days 2 and 3<sup>12</sup>)

‡No additional 5-HT<sub>3</sub> antagonist is required if netupitant-palonosetron combination used.<sup>18</sup> Note palonosetron has a long duration of action (t<sub>1/2</sub> ~44 h in adults).<sup>29</sup>

¶Consider adding olanzapine if nausea / vomiting not controlled with 5-HT<sub>3</sub> antagonist plus dexamethasone plus NK<sub>1</sub> antagonist in previous cycle, especially if delayed nausea is a concern. Note: olanzapine adverse drug reactions including sedation and QTc prolongation, drug interactions and black box warning of increased mortality in elderly patients with dementia. Avoid use of metoclopramide, prochlorperazine, or haloperidol with olanzapine due to increased risk of extrapyramidal symptoms.<sup>15-18</sup>

#For multiday chemotherapy regimens:

- Limited data exist for netupitant-palonosetron. Efficacy has been shown with standard dosing of 1 capsule on day one of a three-day HEC regimen.<sup>28</sup>
- Aprepitant is the NK<sub>1</sub> antagonist of choice for 3 and 5 day regimens. Limited data support dosing oral aprepitant over extended days.<sup>18</sup>
- Suggested regimens based on 5-day cisplatin regimens<sup>22,23</sup>:

aprepitant	5-HT <sub>3</sub> antagonist	dexamethasone
125 mg PO day 1, then 80 mg PO days 2 to 7 <sup>22</sup>	days 1 to 5 <sup>22</sup>	days 1 to 8 <sup>22</sup>
125 mg PO day 3, then 80 mg PO days 4 to 7 <sup>23</sup>	days 1 to 5 <sup>23</sup>	days 1 and 2 <sup>23</sup>

- Suggested regimens based on 3 day MEC and HEC regimens<sup>24</sup>

aprepitant	5-HT <sub>3</sub> antagonist	dexamethasone
125 mg PO day 1, then 80 mg PO days 2 to 5 (i.e., dose 2 additional days post treatment)	On treatment days	days 1 to 5 (i.e., 2 additional days post)

### PROPHYLACTIC ANTIEMETIC REGIMENS FOR ORAL CHEMOTHERAPY<sup>18</sup>:

High or moderate emetogenic risk:

- choose one 5-HT<sub>3</sub> antagonist pre-chemotherapy as listed for HEC/MEC in table above
- post chemotherapy breakthrough dosing as listed for HEC/MEC in table above

Low or minimal (rare) emetogenic risk:

- prn recommended
- if nausea/vomiting occurs:
  - metoclopramide 10 to 20 mg PO pre-chemotherapy then q6h prn **OR**
  - prochlorperazine 10 mg PO pre-chemotherapy then q6h prn (max 40 mg/day) **OR**
  - choose one 5-HT<sub>3</sub> antagonist as listed in table above for low emetogenic risk, given daily prn
- post chemotherapy breakthrough dosing as listed in table above for low/minimal (rare) emetogenic risk

## ADDITIONAL TREATMENT NOTES

- If IV administration of a 5-HT<sub>3</sub> antagonist is clinically indicated, use the same IV dose as the oral dose for ondansetron and granisetron.<sup>3</sup> In contrast, palonosetron 0.5 mg PO is equivalent to palonosetron 0.25 mg IV<sup>17,19</sup>.
- Single doses of 5-HT<sub>3</sub> antagonists are as effective as multiple doses.<sup>3,5</sup>
- First generation 5-HT<sub>3</sub> antagonists (ondansetron, granisetron) are equally effective. Choose based on availability and cost.<sup>1-3,5</sup>
- Palonosetron, a second generation 5-HT<sub>3</sub> antagonist, has a longer duration of action compared to first generation 5-HT<sub>3</sub> antagonists.<sup>25</sup>
- First generation 5-HT<sub>3</sub> antagonists may increase the risk of arrhythmia and Torsade de Pointes in patients:
  - with congenital long QT syndrome, congestive heart failure, or bradyarrhythmias
  - with pre-existing hypokalemia or hypomagnesemia,
  - using medications that prolong QT interval or cardiotoxic chemotherapy.ECG monitoring is recommended in the above patients.<sup>13,20</sup>
- Except for highly emetogenic chemotherapy, a corticosteroid *alone* is the cornerstone of therapy for prevention of delayed nausea and vomiting. There is no role for the routine use of 5-HT<sub>3</sub> antagonists more than 24 hours after chemotherapy.<sup>1-3,6</sup>
- Currently available NK<sub>1</sub> antagonists are equally effective.<sup>18,19</sup>
- Olanzapine may be included on days 1 to 4 of HEC or on days 1 to 3 of MEC for additional control of delayed nausea.<sup>15-18</sup> A lower dose of 2.5 to 5 mg should be considered for elderly and over-sedated patients.<sup>30,31</sup> Other cautions include:
  - Increased risk of death in elderly patients with dementia related psychosis<sup>2</sup>
  - Concomitant administration of parenteral olanzapine and parenteral benzodiazepine is not recommended (toxicity may occur regardless of route)<sup>18</sup>
  - QTc prolongation (see above monitoring recommendations for 5-HT<sub>3</sub> antagonists)
  - Sedation, most notable on day 2
  - Fall risk
  - Extrapyramidal symptoms
- Single-agent palonosetron is not covered by PharmaCare.<sup>27</sup>

## DETERMINING EMETOGENICITY OF CHEMOTHERAPY

- Emetogenicity<sup>18</sup>: percentage of patients who will experience acute emesis if not treated.
  - high = greater than 90%
  - moderate = 30% to 90%
  - low = 10% to less than 30%
  - minimal (rare) = less than 10%
- Single agent chemotherapy: consult [Cancer Drug Manual](#)
- Combination chemotherapy:
  - Consult chemotherapy protocol.
  - If emetogenicity is not specified, consult [Cancer Drug Manual](#)
  - Treat for the most emetogenic agent<sup>1</sup> OR use Hesketh Algorithm.

## HESKETH ALGORITHM<sup>7</sup>

- Identify the most highly emetogenic agent in the combination, then add the contribution of other agents using the following rules:
  - high/moderate: increase emetogenicity of the combination by one level per agent.
  - low: increase emetogenicity of the combination by one level, regardless of how many such agents are added.
  - rare: do not contribute.

## TREATMENT FAILURES

If a patient experiences nausea or vomiting despite optimal prophylactic therapy, complete steps 1, 2, and 3 as follows:

1. Rule out or treat other causes of nausea and vomiting:
  - intestinal obstruction,<sup>1,2</sup> gastroparesis,<sup>2</sup> gastritis<sup>1</sup>
  - medications (pain meds, bronchodilators)<sup>1,2</sup>
  - brain metastases<sup>1,2</sup>
  - vestibular dysfunction<sup>2</sup>
  - electrolyte imbalance,<sup>2</sup> uremia<sup>2</sup>
  - infection<sup>1</sup>
2. Control this episode of nausea and vomiting.
  - Approach to treatment of vomiting<sup>3,18</sup>:
    - give additional antiemetic agent from a different class if vomiting/retching occurs while on antiemetics
    - give 5-HT<sub>3</sub> antagonist +/- dexamethasone if vomiting/retching occurs after antiemetics are finished
    - use rectal, parenteral or sublingual route of administration
    - use around-the-clock dosing rather than prn until vomiting stops
    - monitor and correct hydration and electrolytes as required
    - consider admission to hospital

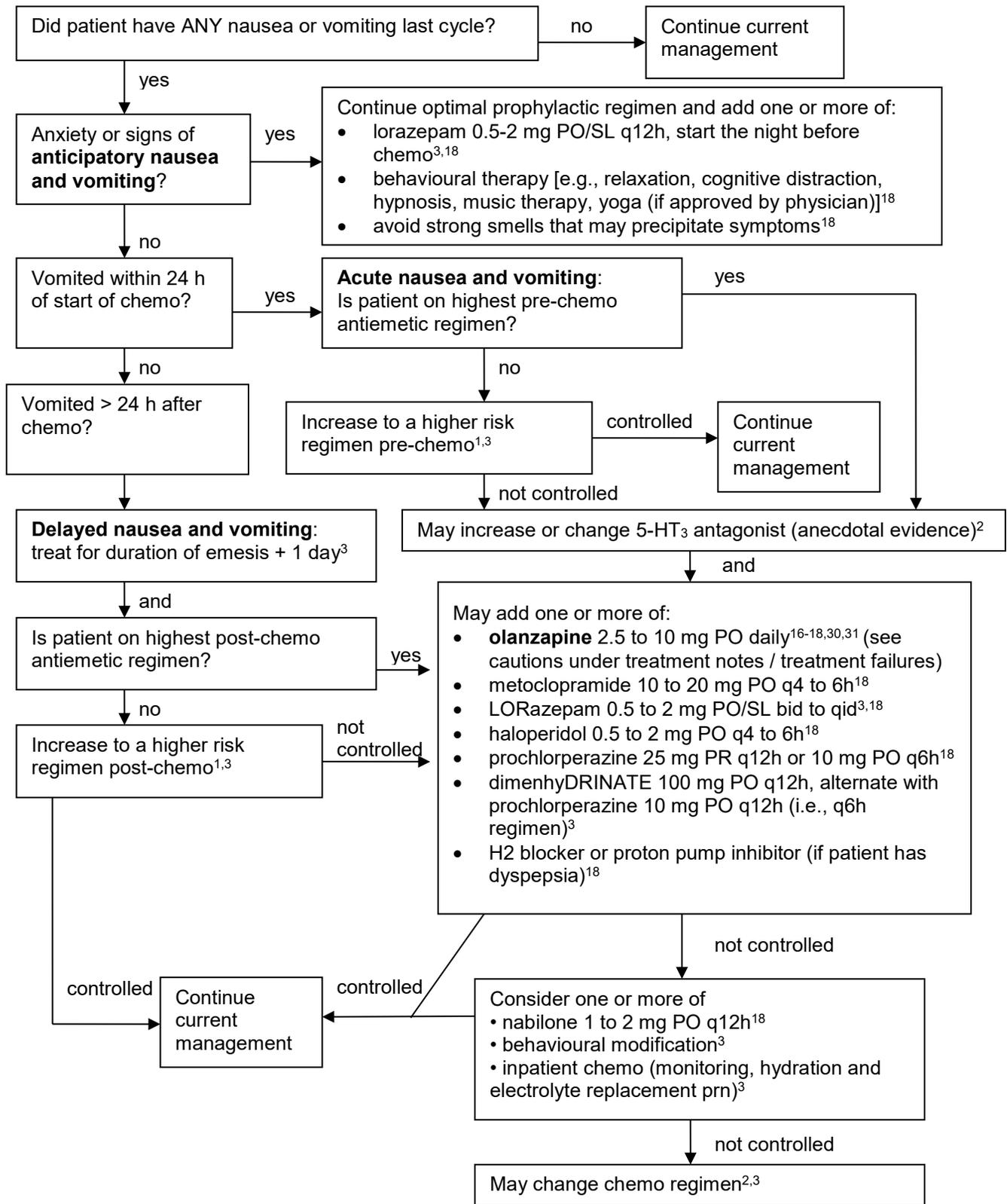
### Possible additional ongoing antiemetics to use if patient is:

vomiting	nauseated*
haloperidol 0.5 to 2 mg PO/IV every 4 to 6 hours <sup>18</sup>	olanzapine 2.5 to 10 mg PO daily (if not previously given and if not using metoclopramide, prochlorperazine or haloperidol) <sup>17,18,30,31</sup>
nabilone 1 to 2 mg PO bid <sup>18</sup>	dimenhyDRINATE 100 mg PO every 12 hours alternating with prochlorperazine 10 mg PO every 12 hours (for a q6h regimen) <sup>3</sup>
	prochlorperazine 25 mg PR every 12 hours or 10 mg PO/IV every 6 hours <sup>18</sup>
	metoclopramide 10 to 20 mg PO every 4 to 6 hours <sup>18</sup>
	nabilone 1 to 2 mg PO bid <sup>18</sup>

\*5-HT<sub>3</sub> antagonist plus dexamethasone if above choices are ineffective<sup>3</sup>

3. Plan prophylactic regimen for next cycle using Figure 1.

**Figure 1. SUBSEQUENT ANTIEMETIC REGIMENS AFTER TREATMENT FAILURE**



**Call Dr. Wendie den Brok or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

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