ANTIEMETIC TREATMENT

ONDANSETRON DOSING – ACUTE SETTING

Ondansetron was the first 5-HT_3 antagonist introduced to the market, and has been extensively evaluated in clinical trials for the prevention of nausea and vomiting in the acute phase. Ondansetron has been evaluated in the management of nausea and vomiting in both highly- and moderately emetogenic regimens.

The recommended use of **ondansetron** for the prevention of nausea and vomiting in the acute setting is as follows:

Level of Emetogenicity	ACUTE Nausea and Vomiting
HIGH (Level 5)	24 mg PO x 1 dose *OR* 8 mg IV x 1 dose *OR* 0.15 mg/kg
MODERATE (Level 3 and 4)	16 mg PO x 1 dose *OR* 8 mg PO BID x 2 doses 8 mg IV x 1 dose *OR* 0.15 mg/kg

Ondansetron has been compared to several other 5-HT_3 antagonists and is felt overall to be equivalent to dolasetron and granisetron. In a trial comparing ondansetron to palonosetron, the results were superior among palonosetron recipients, however the trial did not permit repeat dosing of ondansetron, and furthermore the use of dexamethasone was not permitted. The cooperative groups (ASCO, ASHP, MASCC, and the Perugia Consensus Recommendations) consider ondansetron, granisetron, and dolasetron interchangeable.

<u>Dosing:</u>

Ondansetron is FDA approved as a single dose of 24 mg orally, 30 minutes prior to highly emetogenic chemotherapy and 8 mg PO twice daily for moderately emetogenic chemotherapy. If administering agents intravenously, the FDA approved dose of ondansetron intravenously for both highly and moderately emetogenic chemotherapy is 32 mg IV (or 0.15 mg/kg) as a short IV infusion over 15 minutes, 30 minutes prior to chemotherapy. Despite the FDA approved dosing, consensus guidelines support the use of lower doses as indicated in the table above based on updated clinical data, and the higher dose should almost never be used. The original clinical trials with ondansetron were performed with a dose of 8mg as a bolus injection, followed by a continuous infusion of 1 mg/hour, as well as 32 mg IV bolus doses. Over time, comparative clinical trials have demonstrated the effectiveness of lower doses.

The efficacy of ondansetron in the prevention of acute emesis can be improved significantly (10 – 30%) when combined with dexamethasone; therefore addition of a corticosteroid should always be considered. The dose of corticosteroid varies according to the emetogenicity of the regimen.

DOLASETRON DOSING – ACUTE SETTING

Dolasetron has been extensively evaluated in clinical trials for the prevention of nausea and vomiting in the acute phase. Dolasetron has been evaluated in the management of nausea and vomiting in both highly- and moderately emetogenic regimens.

The recommended use of **dolasetron** for the prevention of nausea and vomiting in the acute setting is as follows:

Level of Emetogenicity	ACUTE Nausea and Vomiting
Moderate (level 3 and 4) and High (Level 5)	100 mg or 0.18 mg/kg IV x 1 dose; *OR* 100 mg PO x 1 dose

Dolasetron has been compared to several other 5-HT_3 antagonists and is felt overall to be equivalent to granisetron and ondansetron. In a trial comparing palonosetron to dolasetron in the prevention of acute nausea and vomiting following emetogenic chemotherapy, both palonosetron and dolasetron were not statistically different. The cooperative groups (ASCO, ASHP, MASCC, and the Perugia Consensus Recommendations) consider ondansetron, dolasetron and granisetron interchangeable.

Dosing:

Dolasetron is FDA approved at a dose of 1.8 mg/kg or alternatively 100 mg IV over 30 seconds. Dolasetron has been evaluated in a number of different doses. The accepted doses are 1.8 mg/kg for 1 dose or a fixed single-dose of 100 mg x 1 dose. An evaluation of approximately 1600 patients (pooled analysis) receiving a variety of different doses of dolasetron demonstrated that a fixed dose of 100 mg was the optimally effective fixed dose for the prevention of chemotherapy associated nausea and vomiting. A dose finding study comparing a variety of doses of dolasetron has demonstrated that higher doses (100 mg or 200 mg) of dolasetron are more effective than lower doses (25 or 50 mg); however there appears to be no significant difference between the 100 mg and 200 mg doses.

The efficacy of dolasetron in the prevention of acute emesis can be improved significantly (10 – 30%) when combined with dexamethasone; therefore addition of a corticosteroid should always be considered. The dose of corticosteroid varies according to the emetogenicity of the regimen.

GRANISETRON DOSING – ACUTE SETTING

Granisetron has been extensively evaluated in clinical trials for the prevention of nausea and vomiting in the acute phase. Granisetron has been evaluated in the management of nausea and vomiting in both highly- and moderately emetogenic regimens.

The recommended use of **granisetron** for the prevention of nausea and vomiting in the acute setting is as follows:

Level of Emetogenicity	Acute Nausea and Vomiting
MODERATE (Level 3 and 4) and HIGH (Level 5)	2 mg PO x 1 dose ***OR*** 0.01 mg/kg IV x 1 dose ***OR*** 1 mg IV x 1 dose

Granisetron has been compared to several other 5-HT_3 antagonists and is felt overall to be equivalent to dolasetron and ondansetron. To date there are no comparative trials comparing granisetron to the new longer acting 5-HT_3 RA palonosetron. The cooperative groups (ASCO, ASHP, MASCC, and the Perugia Consensus Recommendations) consider ondansetron, granisetron, and dolasetron interchangeable.

Dosing:

Granisetron is FDA approved as a single dose of 10 micrograms/kg intravenously administered undiluted over 30 seconds (or diluted in NS or D_5W over 5 minutes), 30 minutes prior to emetogenic chemotherapy. The FDA approved oral dose is either a single dose of 2 mg on the day of chemotherapy, or a dose of 1 mg orally twice daily on the day of chemotherapy.

The efficacy of granisetron in the prevention of acute emesis can be improved significantly (10 – 30%) when combined with dexamethasone; therefore addition of a corticosteroid should always be considered. The dose of corticosteroid varies according to the emetogenicity of the regimen.

PALONOSETRON DOSING – ACUTE SETTING

Palonosetron has been evaluated in clinical trials for the prevention of nausea and vomiting in both the acute and delayed phases. It has also been evaluated in the management of nausea and vomiting in both highly- and moderately emetogenic regimens.

The recommended use of **palonosetron** for the prevention of nausea and vomiting in the ACUTE setting is as follows:

Level of Emetogenicity	Day 1	Day 2 – 4
High (Level 5)	0.25 mg IV x 1 dose	No repeat $5HT_3$ RA doses*
Moderate (Level 3 and 4)	0.25 mg IV x 1 dose	No repeat $5HT_3$ RA doses*
Low (Level 2)	Do not use $5HT_3$ RA routinely unless patient is particularly sensitive and has an extensive emesis history	

*NOTE: repeat doses of palonosetron cannot be recommended at this time based on available literature. The long half-life of palonosetron supports once per cycle dosing. The role of this agent in multi-day chemotherapy regimens and in hematopoietic stem cell transplantation is to be determined and is currently being evaluated.

Dosing:

Palonosetron is FDA approved at a dose of 0.25 mg IV over 30 seconds. A trial evaluating the efficacy, safety and pharmacokinetics of palonosetron found the optimal dose to be between 3 micrograms/kg (approximately 0.25 mg) and 10 micrograms/kg (approximately 0.75mg). Subsequent trials comparing lower (0.25 mg) and higher (0.75 mg) doses of palonosetron to other 5 HT_3 RA found higher doses of palonosetron no more effective than lower doses. Therefore doses higher than 0.25 mg IV x 1 CANNOT be recommended.

PALONOSETRON DOSING – DELAYED SETTING

Palonosetron has been evaluated in clinical trials for the prevention of nausea and vomiting in both the acute and delayed phases. It has also been evaluated in the management of nausea and vomiting in both highly- and moderately emetogenic regimens.

The recommended use of **palonosetron** for the prevention of nausea and vomiting in the DELAYED setting is as follows:

Level of Emetogenicity	Day 1	Day 2 – 4
High (Level 5)	Palonosetron is not FDA approved for the prevention of delayed nausea and vomiting associated with highly emetogenic chemotherapy, however a dose can be given prior to chemotherapy on Day 1 to prevent acute nausea and vomiting (which may translate into lower delayed nausea and vomiting rates)	
Moderate (Level 3 and 4)	0.25 mg IV x 1 dose	No repeat $5HT_3$ RA doses*
Low (Level 2)	Do not use $5HT_3$ RA routinely unless patient is particularly sensitive and has an extensive emesis history	

Dosing:

Palonosetron is FDA approved at a dose of 0.25 mg IV over 30 seconds. A trial evaluating the efficacy, safety and pharmacokinetics of palonosetron found the optimal dose to be between 3 micrograms/kg (approximately 0.25 mg) and 10 micrograms/kg (approximately 0.75 mg). Subsequent trials comparing lower (0.25 mg) and higher (0.75 mg) doses of palonosetron to other 5 HT_3 RA found higher doses of palonosetron no more effective than lower doses. Therefore doses higher than 0.25 mg IV x 1 CANNOT be recommended.

Evidence Supporting Use in Delayed Nausea and Vomiting:

A double-blind randomized phase III trial comparing the efficacy of palonosetron 0.25 mg IV versus ondansetron 32 mg IV demonstrated superior complete response rates (defined as no emetic episode and no use of rescue medication) in both the acute (0 – 24 hours) phase (81% vs. 68.6%) and the delayed (24 to 120 hours) phase: 74.1 % versus 55.1% of palonosetron respectively.

APREPITANT DOSING – DELAYED SETTING

Aprepitant has been extensively evaluated in randomized placebo-controlled clinical trials for the prevention of nausea and vomiting in both the acute and delayed phases. It has also been predominantly evaluated in the management of nausea and vomiting associated with highly emetogenic cisplatin-based regimens. The advantage of aprepitant is in the management of delayed nausea and vomiting associated with highly emetogenic chemotherapy.

The maximum efficacy achieved with aprepitant is in combination with a 5-HT_3 RA and a corticosteroid. In this setting it improves control of acute nausea and vomiting by approximately 10 – 15%. In the delayed phase addition of aprepitant to a 5-HT_3 RA and a corticosteroid increases the proportion of patients being free from emesis by 20 – 30%.
The recommended use of aprepitant for the prevention of nausea and vomiting in the DELAYED setting is as follows:

Level of Emetogenicity	Day 1	Day 2 – 4
High (Level 5)	Aprepitant 125 mg PO Dexamethasone 12 mg PO* 5-HT_3 RA IV/PO	Aprepitant 80 mg PO Day 2 and 3 only Dexamethasone 8 mg PO QAM*
Moderate (Level 3 and 4)	Aprepitant 125 mg PO** Dexamethasone 12 mg PO* 5-HT_3 RA IV/PO	Aprepitant 80 mg PO Day 2 and 3 only Dexamethasone 8 mg PO QAM*

*The dose of dexamethasone must be decreased when used in combination with aprepitant due to an interaction resulting in increased dexamethasone concentrations and consequent complications;
**Aprepitant is only recommended for the following moderately emetogenic regimen: combinations of an anthracycline and cyclophosphamide.

Dosing:

Aprepitant is FDA approved at a dose of 125 mg by mouth on Day 1 (1 hour prior to chemotherapy), followed by 80 mg orally on Day 2 and Day 3. It is FDA approved to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin. It is also FDA approved to prevent nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. A variety of doses were evaluated in earlier clinical trials, however a dose of 125 mg, followed by 80mg was as efficacious as the higher doses of 375 mg followed by 250 mg.

LOW EMETIC RISK CHEMOTHERAPY (HESKETH LEVEL 2)
RECOMMENDED ANTIEMETIC REGIMEN

PREVENTION of ACUTE and DELAYED nausea and vomiting (0 – 24 hours post-chemotherapy)

Each Day of Chemotherapy*
Dexamethasone 4 – 8 mg PO/IV daily (PREFERRED) ***OR***
Promethazine 12.5 – 50 mg PO/PR/IV Q6H PRN ***OR***
Prochlorperazine 10 mg PO/IV Q4 – 6H ***OR***
Metoclopramide 20 – 40 mg PO/IV Q6H PRN ± Diphenhydramine 25 – 50 mg PO/IV Q4-6H PRN
± Lorazepam 0.5 – 2 mg PO/SL/IV Q4-6H PRN

* Preferred route of administration is orally. If patient unable to tolerate the oral route, then IV medication should be administered.

TREATMENT of BREAKTHROUGH nausea and vomiting

If breakthrough emesis occurs while receiving preventive therapy, options include the following (choose agent(s) that were not used in the prophylaxis strategy):

Metoclopramide [Reglan®]*0.5 – 1 mg/kg PO/ IV Q 4 – 6H for 24 – 48 hours ± **Diphenhydramine [Benadryl®]** 25 – 50 mg PO/ IV Q 4 – 6 H for 24 – 48 hours (for dystonia or akathisia)
Phenothiazines: **Prochlorperazine [Compazine®]** 10 – 20 mg PO/ IV Q 4 – 6 H OR 25 mg PR# Q 12H for 24 – 48 hours **Promethazine [Phenergan®]** 12.5 – 25 mg PO/ IV OR 25 mg PR Q 4-6 H for 24 – 48 hours
Lorazepam [Ativan®] 0.5 – 2 mg PO/ SL/ IV Q 4 – 6 H (appropriate for N/V caused by anticipatory reasons). Use as adjunctive agent.
Haloperidol [Haldol®] 0.5 – 1 mg PO/ IV Q 6 H for 24 – 48 hours

*Avoid if patient experiencing diarrhea; #Avoid PR route of administration in neutropenic patients.

MODERATELY EMETOGENIC CHEMOTHERAPY (HESKETH LEVEL 3 AND 4) RECOMMENDED ANTIEMETIC REGIMEN

PREVENTION of ACUTE and DELAYED nausea and vomiting (0 – 24 hours post-chemotherapy)

Day 1
5-HT_3 RA PO*/IV (see below for doses)
Dexamethasone 20 mg PO (NOTE: if using aprepitant for a regimen containing an anthracycline and cyclophosphamide reduce the dose of dexamethasone to 12 mg)
Aprepitant 125 mg PO (only recommended for anthracycline plus cyclophosphamide containing regimens within this level of emetogenicity)

Day 2 – 3
Options 1: Dexamethasone 8 mg PO QD **Option 2:** 5-HT_3 RA (daily)**
Aprepitant 80 mg/day on Day 2 and 3 for patients receiving combinations of anthracyclines and cyclophosphamide

*Preferred route of administration is orally. If patient unable to tolerate the oral route, then IV medication should be administered; **If palonosetron was prescribed as part of the prophylaxis against acute nausea and vomiting, a 5-HT_3 RA should not be re-administered for delayed prophylaxis due to the long half-life of palonosetron.

5-HT_3-RA Choices:

Drug	Dose	Route
Dolasetron	100 mg x 1 dose	PO
	100 mg or 1.8 mg/kg x 1 dose	IV
Granisetron	2 mg x 1 dose	PO
	1 mg (or 10 micrograms/kg) x 1 dose	IV
Ondansetron	16 mg x 1 dose; *OR*	PO
	8 mg PO BID x 2 doses	PO
	8 mg or 0.15 mg/kg x 1 dose	IV
Palonosetron**	0.25 mg x 1 dose	IV

**If palonosetron was prescribed as part of the prophylaxis against acute nausea and vomiting, a 5-HT_3 RA should not be re-administered for delayed prophylaxis due to the long half-life of palonosetron.

TREATMENT of BREAKTHROUGH nausea and vomiting

If breakthrough emesis occurs while receiving preventive therapy, options include the following (choosing an agent that was not used in the prophylaxis strategy):

Metoclopramide [Reglan®]*0.5 – 1 mg/kg PO/ IV Q 4 – 6H for 24 – 48 hours ±
Diphenhydramine [Benadryl®] 25 – 50 mg PO/ IV Q 4 – 6 H for 24 – 48 hours (for dystonia or akathisia)

For **delayed breakthrough nausea and vomiting** use the following:
Metoclopramide [Reglan®]*0.5 mg/kg PO/ IV QID (rounded to nearest 10mg) for 2 – 4 days ±
Diphenhydramine [Benadryl®] 25 – 50 mg PO/ IV ID for 2 – 4 days (for dystonia or akathisia) PLUS
Dexamethasone 8 mg PO/IV BID for 2 – 4 days

Phenothiazines:
- **Prochlorperazine [Compazine®]** 10 – 20 mg PO/ IV Q 4 – 6 H OR 25 mg PR# Q 12H for 24 – 48 hours
- **Promethazine [Phenergan®]** 12.5 – 25 mg PO/ IV OR 25 mg PR# Q 4-6 H for 24 – 48 hours

Lorazepam [Ativan®] 0.5 – 2 mg PO/ SL/ IV Q 4 – 6 H (appropriate for N/V caused by anticipatory reasons). Use as adjunctive agent.

Haloperidol [Haldol®] 0.5 – 1 mg PO/ IV Q 6 H for 24 – 48 hours

HIGHLY EMETOGENIC CHEMOTHERAPY (HESKETH LEVEL 5) RECOMMENDED ANTIEMETIC REGIMEN

PREVENTION of ACUTE and DELAYED nausea and vomiting (0 – 24 hours post-chemotherapy)

ACUTE	DELAYED	
Day 1	**Day 2**	**Day 3**
Aprepitant 125 mg PO	Aprepitant 80 mg PO	Aprepitant 80 mg PO
5-HT_3 RA PO*/IV (see below for doses)	Nil	Nil
Dexamethasone 12 mg PO**	Dexamethasone 8 mg PO	Dexamethasone 8 mg PO

*Preferred route of administration is orally. If patient unable to tolerate the oral route, then IV medication should be administered.
**If aprepitant is not being prescribed as part of the acute antiemetic regimen, increase the dose of dexamethasone to 20 mg. The 12 mg dose is required with aprepitant due to a drug interaction.

5-HT_3-RA Choices:

Drug	Dose	Route
Dolasetron	100 mg x 1 dose	PO
	100 mg or 1.8 mg/kg x 1 dose	IV
Granisetron	2 mg x 1 dose	PO
	1 mg BID x 2 doses	PO
	1 mg (or 10 micrograms/kg) x 1 dose	IV
Ondansetron	24 mg x 1 dose	PO
	8 mg or 0.15 mg/kg x 1 dose	IV
Palonosetron	0.25 mg x 1 dose	IV

TREATMENT of BREAKTHROUGH nausea and vomiting

If breakthrough emesis occurs while receiving preventive therapy, options include the following (choose agent(s) that were not used in the prophylaxis strategy):

Metoclopramide [Reglan®]*0.5 – 1 mg/kg PO/ IV Q 4 – 6H for 24 – 48 hours ±
Diphenhydramine [Benadryl®] 25 – 50 mg PO/ IV Q 4 – 6 H for 24 – 48 hours (for dystonia or akathisia)

For **delayed breakthrough nausea and vomiting** use the following:
Metoclopramide [Reglan®]*0.5 mg/kg PO/ IV QID (rounded to nearest 10mg) for 2 – 4 days ±
Diphenhydramine [Benadryl®] 25 – 50 mg PO/ IV ID for 2 – 4 days (for dystonia or akathisia) PLUS
Dexamethasone 8 mg PO/IV BID for 2 – 4 days

Phenothiazines:
- **Prochlorperazine [Compazine®]** 10 – 20 mg PO/ IV Q 4 – 6 H OR 25 mg PR# Q 12H for 24 – 48 hours
- **Promethazine [Phenergan®]** 12.5 – 25 mg PO/ IV OR 25 mg PR# Q 4-6 H for 24 – 48 hours

Lorazepam [Ativan®] 0.5 – 2 mg PO/ SL/ IV Q 4 – 6 H (appropriate for N/V caused by anticipatory reasons). Use as adjunctive agent)

Haloperidol [Haldol®] 0.5 – 1 mg PO/ IV Q 6 H for 24 – 48 hours

*Avoid if using concurrently for prevention or if patient experiencing diarrhea; #Avoid PR route of administration in neutropenic patients.

ANTICIPATORY NAUSEA AND VOMITING

Extensive pre-chemotherapy education and alleviation of patient's fears are critical in order to minimize or eliminate potential difficulties with nausea and/or vomiting.

Optimum prevention/treatment of acute nausea and vomiting is imperative in the prevention of anticipatory nausea and vomiting.

TREATMENT CHOICES:
Lorazepam 0.5 - 3 mg PO at bedtime, and 0.5 - 3 mg PO/SL/IV upon arrival to the office/clinic.
OR
Alprazolam 0.5 - 2 mg PO at bedtime and upon arrival to the office/clinic prior to chemotherapy administration.

RADIATION INDUCED EMESIS

RISK LEVEL	IRRADIATED AREA	ANTIEMETIC GUIDELINES	MASCC EVIDENCE (LEVEL OF SCIENTIFIC CONFIDENCE/LEVEL OF CONSENSUS)	ASCO EVIDENCE (TYPE OF EVIDENCE/GRADE OF RECOMMENDATION)
High (> 90%)	Total body irradiation	Prophylaxis with: 1: A 5-HT_3 antagonist prior to each fraction (and 24 hours after).	1- High/High	1: II/B
		2: +/- Dexamethasone	2- Moderate/High	2: III/C
Moderate (60-90%)	Upper abdomen (intermediate risk) hemibody irradiation, upper abdomen, abdominal-pelvic, mantle, craniospinal irradiation, and cranial radiosurgery	Prophylaxis with a 5-HT_3 antagonist prior to each fraction.	High/High	II/A
Low (30-60%)	1: Lower thorax region and pelvis	Prophylaxis with a 5-HT_3 antagonists prior to each fraction	1- Moderate/High	1: III/B
	2: Cranium (radiosurgery) and craniospinal		2- Low/High	2: IV/D
Minimal (< 30%)	Head and neck, extremities, cranium and breast	Rescue with dopamine receptor antagonists or 5-HT_3 antagonists. Antiemetics should be continued prophylactically for reach remaining radiation treatment day	Low/High	IV/D

References: Feyer PC, et al. *Support Care Cancer* 2005;13:122 - 8; Kris MG, et al. *J Clin Oncol* 2006;24:2932 - 47; Erratum in *J Clin Oncol* 2006;24:5341 - 2.