

## American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006

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### A B S T R A C T

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#### Purpose

To update the 1999 American Society of Clinical Oncology guideline for antiemetics in oncology.

#### Update Methodology

The Update Committee completed a review and analysis of data published from 1998 thru February 2006. The literature review focused on published randomized controlled trials, and systematic reviews and meta-analyses of published phase II and phase III randomized controlled trials.

#### Recommendations

The three-drug combination of a 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) serotonin receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy of high emetic risk. For persons receiving chemotherapy of high emetic risk, there is no group of patients for whom agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT<sub>3</sub> serotonin receptor antagonists, neurokinin-1 receptor antagonists, and dexamethasone. The three-drug combination of a 5-HT<sub>3</sub> receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving an anthracycline and cyclophosphamide. For patients receiving other chemotherapy of moderate emetic risk, the Update Committee continues to recommend the two-drug combination of a 5-HT<sub>3</sub> receptor serotonin antagonist and dexamethasone. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended for the prevention of delayed emesis. The Update Committee no longer recommends the combination of a 5-HT<sub>3</sub> serotonin receptor antagonist and dexamethasone for the prevention of delayed emesis after chemotherapeutic agents of high emetic risk.

#### Conclusion

The Update Committee recommends that clinicians administer antiemetics while considering patients' emetic risk categories and other characteristics.

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#### INTRODUCTION

The American Society of Clinical Oncology (ASCO) published evidence-based clinical practice guidelines for the use of antiemetics in 1999.<sup>1</sup> As part of ASCO's guideline process, all guideline documents are updated periodically by an Update Committee of the responsible Expert Panel (Appendix 1).<sup>2</sup>

The entire Update Committee met once to discuss strategy and to assign roles for the update. A writing committee (M.G.K., P.J.H., S.M.G., and M.R.S.) collated different sections of the update prepared by the Update Committee members and edited the manuscript. A final draft was circulated to the full Update Committee for review and approval. The document was then reviewed and approved by ASCO's Health Services Committee and by the ASCO Board of Directors.

#### UPDATE METHODOLOGY

For the 2006 update, the Update Committee completed the review and analysis of data published since 1998. Computerized literature search of MEDLINE (National Library of Medicine, Bethesda, MD) and the Cochrane Collaboration Library were performed. Details of the literature search and methods are described in Appendix 2.

The Update Committee's literature review focused on published randomized, controlled trials and systematic reviews and meta-analyses of published phase II and phase III randomized, controlled trials. The electronic literature searches identified a systematic review on aprepitant,<sup>3</sup> a systematic review and meta-analysis on the role of neurokinin-1 (NK<sub>1</sub>) receptor antagonists in the prevention of emesis and nausea due to high-dose chemotherapy

with cisplatin,<sup>4</sup> a meta-analysis of randomized trials assessing the efficacy of dexamethasone in controlling chemotherapy-induced nausea and vomiting,<sup>5</sup> and three systematic reviews and meta-analyses of 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) serotonin receptor antagonists.<sup>4,6,7</sup> Prepublication copies of two additional systematic reviews were made available to the Update Committee by the Cancer Care Ontario Program in Evidence-Based Care<sup>8</sup> and the Oregon Evidence-Based Practice Center, respectively.<sup>9</sup>

The Update Committee also considered carefully the guidelines and consensus statements that emerged from the International Antiemetic Consensus Conference, hosted by the Multinational Association of Supportive Care in Cancer (MASCC; Perugia, Italy), in March 2004.<sup>10,11</sup> This meeting established a guideline process conducted by representatives from nine international oncology organizations, including ASCO. Seven members of the original ASCO Antiemetic Guideline Expert Panel participated (R.C.-S., P.F., R.J.G., S.M.G., P.J.H., M.G.K., J.M.K.). The methodology for this guideline process was based on a literature review up to March 2004 using MEDLINE and other databases, with evaluation of the evidence by 23 oncology professionals in clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology.<sup>11</sup> The consensus statements and treatment guidelines coming from this meeting have been published on the Internet (mascc.org) and in print.<sup>12-19</sup> An overall summary of the meeting has been published as well.<sup>20</sup> It was agreed that each of the nine oncology organizations participating in the meeting would also publish the meeting results in whole or in part with their individual antiemetic guidelines. Although the group believed that the guidelines coming from each society would differ (given that each organization has a distinct constituency and mission), it was hoped that because many groups participated in the deliberations and guideline creation, fewer discrepancies among the individual documents would result. Wherever possible, the ASCO Antiemetic Guideline Update Committee used the consensus statements and guidelines from the MASCC process to supplement other resources and to assist them in the preparation of this update.

The guideline update presents the “current recommendation” for each of the topics considered in the original guideline: “no change” is indicated if a recommendation has not been revised after analysis of the literature search and Update Committee review (Tables 1 to 4).

This section is followed by a 2006 literature update section. Whenever possible, the Update Committee preserved the organizing framework of the 1999 guideline document. Recommendations and supporting evidence for major new topics, such as aprepitant and palonosetron, have been distributed in the appropriate sections of the text.

ASCO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.

## 2006 PRACTICE RECOMMENDATIONS

### I. EMESIS CAUSED BY INTRAVENOUSLY ADMINISTERED ANTINEOPLASTIC AGENTS

Emesis, measured by counting the number of vomiting episodes after treatment, is the most important clinical trial end point for studies of antiemetic drugs. Studies have documented that the occurrence of complete response (no emetic episodes and no rescue medications administered after antineoplastic therapy) is a highly accurate and reliable measure.<sup>21-23</sup> This outcome has also been demonstrated to correlate with the patients' perception of emesis. Nausea (the perception that emesis may occur) can be judged only by the patient. Although the incidence of nausea correlates with the incidence of vomiting,<sup>24</sup> nausea generally occurs more frequently than vomiting. The Update Committee recommends the use of complete response for the guideline development process. Recent trials of aprepitant and palonosetron in patients receiving the therapies of high or moderate emetic risk have recorded the incidence of vomiting, use of rescue therapy, and nausea for 5 days after antineoplastic treatment. The Update Committee recommends that the assessment of vomiting (no emesis and no rescue administered) and nausea for the 5 days after

**Table 1.** Summary of Recommendations for Antiemetics in Oncology: Antiemetic Agents

Recommendation	Category	Current Recommendations
5-HT <sub>3</sub> serotonin receptor antagonists	Agent equivalence	At equivalent doses for the prevention of acute emesis, 5-HT <sub>3</sub> serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably.
	Drug dosage	No change from the original guideline. Use only established doses.
	Drug schedule	No change from the original guideline. Single doses are preferred.
	Route of administration	No change from the original guideline. At biologically equivalent doses, oral formulations are equally effective and safe as intravenous.
Corticosteroids	Agent equivalence and route of administration	No change from the original guideline. At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably. Dexamethasone is preferred because of its extensive clinical study and wide availability.
	Drug dose and schedule	Single doses of dexamethasone are recommended.
NK <sub>1</sub> receptor antagonist (aprepitant)	Drug dose and schedule	Only the established dose and schedule of aprepitant should be used.

Abbreviations: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3; NK<sub>1</sub>, neurokinin 1.

**Table 2.** Summary of Recommendations for Antiemetics in Oncology: Antiemetic Regimens

Recommendation Category	Current Recommendations
Specific emetic risk categories	<p><i>High (&gt; 90%) emetic risk.</i> The three-drug combination of a 5-HT<sub>3</sub> serotonin receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended. The Update Committee no longer recommends the combination of a 5-HT<sub>3</sub> serotonin receptor antagonist and dexamethasone on days 2 and 3.</p> <p><i>Moderate (&gt; 30% to 90%) emetic risk.</i> The three-drug combination of a 5-HT<sub>3</sub> receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving AC. For patients receiving chemotherapy of moderate emetic risk other than AC, we recommend the two-drug combination of a 5-HT<sub>3</sub> receptor serotonin antagonist and dexamethasone. In patients receiving AC, aprepitant as a single agent is recommended on days 2 and 3. For all other chemotherapies of moderate emetic risk, single-agent dexamethasone or a 5-HT<sub>3</sub> serotonin receptor antagonist is suggested for the prevention of emesis on days 2 and 3.</p> <p><i>Low (10% to 30%) emetic risk.</i> Dexamethasone 8 mg is suggested. No routine preventive use of antiemetics for delayed emesis is suggested.</p> <p><i>Minimal (&lt; 10%) emetic risk.</i> No change from the original guideline. No antiemetic should be administered routinely before or after chemotherapy.</p> <p><i>Combination chemotherapy.</i> No change from the original guideline. Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.</p> <p><i>Multiple consecutive days of chemotherapy.</i> No change from the original guideline. It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy and for 2 days after, if appropriate.</p> <p><i>Antiemetic agents: lower therapeutic index.</i> For persons receiving chemotherapy of high emetic risk, there is no group of patients for whom agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT<sub>3</sub> serotonin receptor antagonists, NK<sub>1</sub> receptor antagonists, and dexamethasone.</p> <p><i>Antiemetic agents: adjunctive drugs.</i> Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs, but are not recommended as single agents.</p> <p><i>Antiemetic agents: combinations of antiemetics.</i> It is recommended that 5-HT<sub>3</sub> serotonin receptor antagonists be administered with dexamethasone and aprepitant in patients receiving chemotherapy of high emetic risk and in patients receiving AC. A 5-HT<sub>3</sub> serotonin receptor antagonist combined with dexamethasone should be used in patients receiving agents of moderate emetic risk other than AC.</p>

Abbreviations: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3; NK<sub>1</sub>, neurokinin 1; AC, anthracycline and cyclophosphamide.

treatment be standard primary end points for antiemetic clinical trials in oncology.

**A. VOMITING OCCURRING 0 TO 24 HOURS AFTER THERAPY (ACUTE EMESIS)**

**1. Emetic Risk of Antineoplastic Agents: Emetic Risk Categories**

Antineoplastic agents are grouped by the risk of emesis they pose and matched to specific antiemetic regimens designed to prevent the degree of vomiting expected. This process is hindered by the fact that the potential of an administered drug to cause emesis has been established rigorously for only a few agents. By necessity rather than design, categories based on experience rather than on specific data have generally been developed.<sup>25-27</sup> The recent MASCC consensus conference established four emetic risk categories based on the data available.<sup>12</sup> It further endeavored to reconcile the classification schemes in print for intravenous antineoplastic agents (Tables 5 and 6). We have adopted this classification for the 2006 update of the ASCO Guideline for Antiemetics in Oncology.

**2. Antiemetic Agents: Highest Therapeutic Index**

Three classes of agents are in this category: the 5-HT<sub>3</sub> serotonin receptor antagonists, corticosteroids (dexamethasone), and the NK<sub>1</sub> receptor antagonists (aprepitant; Tables 7, 8, and 9). The NK<sub>1</sub> receptor antagonists represent a new class of antiemetics that have become available since the last version of the guideline. Aprepitant is the first member of this class to gain regulatory approval. These three classes of antiemetic agents are highly effective, have few significant adverse

effects when used appropriately, and can be administered safely in combination.

*a. 5-HT<sub>3</sub> Serotonin Receptor Antagonists (dolasetron, granisetron, ondansetron, palonosetron, tropisetron).*

Agent equivalence, drug dosage, drug schedule, and route of administration are discussed separately below. Specific recommendations for differing acute emetic risk settings are given in a later section.

*i. Agent equivalence. Current recommendation.* At equivalent doses for the prevention of acute emesis, 5-HT<sub>3</sub> serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably.

*2006 literature update and discussion.* There are now at least five agents of this class widely available: dolasetron, granisetron, ondansetron, palonosetron, and tropisetron. Multiple, randomized, controlled studies with sufficient patients to estimate precisely differences in outcomes have demonstrated that these agents have equivalent antiemetic activity and safety. These agents also share similar adverse effect patterns, with mild headache, transient asymptomatic elevations of serum aminotransferases, and constipation reported. Dose-limiting effects are rare. Although some differences in adverse effect profiles of the agents have been reported, the clinical relevance—if any—of these differences is not apparent.

A meta-analysis by del Giglio et al<sup>6</sup> of 14 randomized, controlled trials of granisetron versus ondansetron with 6,467 assessable patients, found that these agents have similar efficacy in preventing nausea and emesis. Similar results were observed by Cancer Care Ontario from a systematic review of 12 randomized, controlled trials of ondansetron,

**Table 3.** Summary of Recommendations for Antiemetics in Oncology: Special Emetic Problems

Recommendation Category	Current Recommendations
Emesis in pediatric oncology patients	The combination of a 5-HT <sub>3</sub> antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Due to variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT <sub>3</sub> antagonists than those used in adults may be required for antiemetic protection.
High-dose chemotherapy	No change from original guideline. A 5-HT <sub>3</sub> serotonin receptor antagonist antiemetic combined with dexamethasone is suggested. Aprepitant should be considered although evidence to support its use specifically in these patients is lacking.
Vomiting and nausea despite recommended prophylaxis	No change from original guideline. The Update Committee suggests that clinicians (1) conduct a careful re-evaluation of emetic risk, disease status, concurrent illnesses, and medications; (2) ascertain that the best regimen is being administered for the emetic risk; (3) consider adding an lorazepam or alprazolam to the regimen; and (4) consider substituting a high-dose intravenous metoclopramide for the 5-HT <sub>3</sub> antagonist or adding a dopamine antagonist to the regimen.

Abbreviation: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3.

dolasetron, and granisetron<sup>6</sup>; and from the Oregon Evidence-Based Practice Center's recent systematic review of the range of available 5-HT<sub>3</sub> serotonin receptor antagonists.<sup>9</sup>

Intravenous palonosetron became available in 2003. This agent was developed because of its longer serum half-life (about five times that of other drugs in the class) and higher binding affinity to the 5-HT<sub>3</sub> serotonin receptor. Among patients receiving chemotherapy of moderate emetic risk, single intravenous doses of palonosetron were compared with single intravenous doses of ondansetron<sup>28</sup> and dolasetron<sup>29</sup> in two noninferiority trials. In the latter study, palonosetron was as effective as dolasetron for the prevention of acute emesis.<sup>29</sup> In the former, palonosetron proved superior to ondansetron in the prevention of acute emesis.<sup>28</sup> In both of these trials, patients were also observed from 24 to 120 hours after chemotherapy. They received no additional prophylactic antiemetics. Complete response (no emetic episodes and no use of rescue medications) during this delayed emesis period, was improved by 19% compared with ondansetron ( $P < .001$ ) and 15% compared with dolasetron ( $P = .004$ ) in patients receiving palonosetron 0.25 mg administered before chemotherapy.<sup>28,29</sup> Single intravenous doses of palonosetron and ondansetron were also evaluated in patients receiving cisplatin.<sup>30</sup> Two thirds of the 667 patients participating in this double-blind, randomized trial received corticosteroids as well. For the primary study end point (no emesis and no

rescue antiemetic administered), the palonosetron and ondansetron regimens were equivalent.

The 2006 Antiemetic Update Committee did not designate a preferred 5-HT<sub>3</sub> antagonist. Although palonosetron outperformed ondansetron and dolasetron in several secondary and subgroup analyses in head-to-head comparisons, the primary end point of the three registration trials was noninferiority. That end point was met in all studies. However, there are no prospective trials designed specifically to prove the superiority of palonosetron over any 5-HT<sub>3</sub> antagonist. There are also no prospective trials comparing palonosetron with another 5-HT<sub>3</sub> antagonist when both are combined with dexamethasone. These two-drug regimens were recommended as antiemetics for chemotherapies of both high and moderate emetic risk by the 1999 ASCO Antiemetic Guideline Panel and all other guideline groups, during the time when the single-agent palonosetron comparison trials were designed and conducted. The addition of aprepitant to antiemetic regimens for patients receiving chemotherapies of high emetic risk and anthracycline and cyclophosphamide (AC) further complicates these issues. The superiority question has now evolved to whether or not palonosetron is better than other 5-HT<sub>3</sub> antagonists when they are combined with both dexamethasone and aprepitant. The absence of documentation for the superiority of dolasetron, granisetron, and ondansetron, coupled with the lack of relevant

**Table 4.** Summary of Recommendations for Antiemetics in Oncology: Radiation-Induced Emesis

Recommendation Category	Current Recommendations
High risk: total-body irradiation	No change from original guideline. The Update Committee suggests giving a 5-HT <sub>3</sub> serotonin receptor antagonist with or without a corticosteroid before each fraction and for at least 24 hours after.
Moderate emetic risk: upper abdomen (intermediate risk) hemibody irradiation, upper abdomen, abdominal-pelvic, mantle, craniospinal irradiation, and cranial radiosurgery	The Update Committee recommends a 5-HT <sub>3</sub> serotonin receptor antagonist before each fraction.
Low emetic risk: lower thorax, cranium (radiosurgery), and craniospinal	No change from original guideline. The Update Committee recommends a 5-HT <sub>3</sub> serotonin receptor antagonist before each fraction.
Minimal emetic risk: radiation of breast, head and neck, cranium, and extremities	No change from original guideline. The Update Committee suggests that treatment be administered on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.

Abbreviation: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3.

**Table 5.** Emetic Risk of Intravenously Administered Antineoplastic Agents

Emetic Risk (incidence of emesis without antiemetics)	Agent	
High (> 90%)	Cisplatin	
	Mechlorethamine	
	Streptozotocin	
	Cyclophosphamide $\geq 1,500$ mg/m <sup>2</sup>	
	Carmustine	
	Dacarbazine	
	Dactinomycin	
	Oxaliplatin	
Moderate (30 to 90%)	Cytarabine > 1 g/m <sup>2</sup>	
	Carboplatin	
	Ifosfamide	
	Cyclophosphamide < 1,500 mg/m <sup>2</sup>	
	Doxorubicin	
	Daunorubicin	
	Epirubicin	
	Idarubicin	
	Irinotecan	
	Low (10% to 30%)	Paclitaxel
		Docetaxel
		Mitoxantrone
Topotecan		
Etoposide		
Pemetrexed		
Methotrexate		
Mitomycin		
Gemcitabine		
Cytarabine $\leq 1,000$ mg/m <sup>2</sup>		
Fluorouracil		
Bortezomib		
Cetuximab		
Trastuzumab		
Minimal (< 10%)		Bevacizumab
		Bleomycin
		Busulfan
		2-Chlorodeoxyadenosine
	Fludarabine	
	Rituximab	
	Vinblastine	
	Vincristine	
	Vinorelbine	

**Table 6.** Estimation of Emetic Risk for Intravenous Antineoplastic Agents Categorized According to the 2006 and 1999 Emetic Risk Classification Schemes

Antineoplastic Agent	2006 Emetic Risk Category	1999 Emetic Risk Category
Cisplatin	High	High: cisplatin
Mechlorethamine	High	High: noncisplatin
Streptozotocin	High	High: noncisplatin
Cyclophosphamide > 1,500 mg/m <sup>2</sup>	High	High: noncisplatin
Carmustine	High	High: noncisplatin
Dacarbazine	High	High: noncisplatin
Dactinomycin	High	High: noncisplatin
Oxaliplatin	Moderate	Not included
Cytarabine 1,000 mg/m <sup>2</sup>	Moderate	High: noncisplatin
Carboplatin	Moderate	High: noncisplatin
Ifosfamide	Moderate	High: noncisplatin
Cyclophosphamide < 1,500 mg/m <sup>2</sup>	Moderate	High: noncisplatin
Doxorubicin	Moderate	High: noncisplatin
Daunorubicin	Moderate	High: noncisplatin
Epirubicin	Moderate	High: noncisplatin
Idarubicin	Moderate	High: noncisplatin
Irinotecan	Moderate	Intermediate
Paclitaxel	Low	Intermediate
Docetaxel	Low	Intermediate
Mitoxantrone	Low	Intermediate
Topotecan	Low	Intermediate
Etoposide	Low	Intermediate
Pemetrexed	Low	Not included
Methotrexate	Low	Low
Mitomycin	Low	Intermediate
Gemcitabine	Low	Intermediate
Cytarabine $\leq 1,000$ mg/m <sup>2</sup>	Low	High: noncisplatin
Fluorouracil	Low	Low
Bortezomib	Low	Not included
Cetuximab	Low	Not included
Trastuzumab	Low	Not included
Bevacizumab	Minimal	Not included
Bleomycin	Minimal	Low
2-Chlorodeoxyadenosine	Minimal	Low
Fludarabine	Minimal	Low
Rituximab	Minimal	Not included
Vinblastine	Minimal	Low
Vincristine	Minimal	Low
Vinorelbine	Minimal	Not included

comparison data demonstrating the superiority of palonosetron over the three other drugs in the class in the combinations, which are the standard of care, has led the Update Committee to make the recommendation above.

*ii. Drug dosage. Current recommendation.* Only established doses of all agents are recommended. There is no change from the original guideline.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for the update for drug dosage. The del Giglio et al<sup>6</sup> meta-analysis did not address drug dosage. The Cancer Care Ontario systematic review and guideline reviewed the evidence on drug dose. They noted that dose varied widely across studies. Recommendations regarding dose were considered outside of the scope of the guideline.<sup>4</sup>

*iii. Drug schedule. Current recommendation.* Single doses are preferred. There is no change from the original guideline.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for the update for drug schedule. The del Giglio et al<sup>6</sup> meta-analysis did not address drug schedule. The Cancer Care Ontario systematic review and guideline authors noted that drug schedule varied widely across studies.<sup>4</sup> Recommendations regarding schedule were considered outside of the scope of the guideline.

*iv. Route of administration. Current recommendation.* At biologically equivalent doses, oral formulations are equally effective and safe as intravenous antiemetics. There is no change from the original guideline.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for the update for route of administration. The del Giglio et al<sup>6</sup> meta-analysis did not address route of administration. The Cancer Care Ontario systematic review and guideline reviewed the evidence on route of administration. They

**Table 7.** Drug Regimens for the Prevention of Chemotherapy-Induced Emesis by Emetic Risk Category (see Tables 8 and 9 for doses, schedules, and routes of administration)

Emetic Risk Category (incidence of emesis without antiemetics)	Antiemetic Regimens and Schedules
High (> 90%)	5-HT <sub>3</sub> serotonin receptor antagonist: day 1 Dexamethasone: days 1, 2, 3 Aprepitant: days 1, 2, 3
Moderate (30% to 90%)	5-HT <sub>3</sub> serotonin receptor antagonist: day 1 Dexamethasone: day 1 (Aprepitant: days 1, 2, 3)*
Low (10% to 30%)	Dexamethasone: day 1
Minimal (< 10%)	Prescribe as needed (see text for details of agent selection)

Abbreviation: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3.

\*For patients receiving a combination of an anthracycline and cyclophosphamide.

believed that data were insufficient to make a recommendation regarding the equivalence of intravenous and oral 5-HT<sub>3</sub> serotonin receptor antagonists.<sup>4</sup>

*b. Corticosteroids (dexamethasone and methylprednisolone).* Corticosteroids also have a high therapeutic index when used to prevent chemotherapy-induced emesis. They are among the most frequently used antiemetics; single-agent use is appropriate in patients receiving chemotherapies of low emetic risk. Dexamethasone is especially valuable when administered in combination with 5-HT<sub>3</sub> serotonin receptor antagonists and aprepitant in patients receiving chemotherapy of high or moderate emetic risk.

*i. Agent equivalence and route of administration. Current recommendation.* At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably. There is no change from the original guideline.

*2006 literature update.* The corticosteroids most frequently studied as antiemetics are dexamethasone and methylprednisolone. Although efficacy has been reported with both agents, there have been no comparison trials. Dexamethasone has the advantages of being available in many dosage formulations and accessible in generic forms

in many countries. There are no formal trials comparing oral with parenteral corticosteroids. The Update Committee recommends dexamethasone because of the extensive published experience with this agent. A meta-analysis of 32 randomized trials (with 42 relevant comparisons and a total of 5,613 patients) assessing the efficacy of dexamethasone in controlling chemotherapy-induced nausea and vomiting found that dexamethasone was superior to placebo or no treatment for complete protection from both acute emesis (risk ratio [RR] = 1.30; 95% CI, 1.24 to 1.37) and delayed emesis (RR = 1.30; 95% CI, 1.21 to 1.39).<sup>5</sup> Similar results were obtained for the nausea outcome and for the subset of 18 comparisons that included administration of a 5-HT<sub>3</sub> serotonin receptor antagonist in both trial arms.

*ii. Drug dose and schedule. Current recommendation.* Single daily doses of corticosteroids are recommended. There is no change from the original guideline.

*2006 literature update and discussion.* The Update Committee recommends dexamethasone because it is the corticosteroid most extensively studied and is widely available. One randomized study demonstrated improved efficacy and equivalent adverse effects with dexamethasone administered at 20 mg (with 5-HT<sub>3</sub> serotonin receptor antagonists) compared with dexamethasone at lower doses in patients receiving chemotherapy of high emetic risk.<sup>31</sup> Adverse effects of single dexamethasone doses are rare, although elevations of serum glucose levels, epigastric burning, and sleep disturbances occur.

Another randomized study by the same group evaluated patients receiving chemotherapy of moderate emetic risk (anthracyclines, carboplatin, or cyclophosphamide) and concluded that the appropriate dose of dexamethasone administered in combination with a 5-HT<sub>3</sub> serotonin receptor antagonist for the prevention of acute emesis was 8 mg administered once before chemotherapy.<sup>32</sup> No additional benefit was seen with a single 24-mg pretreatment dose or when 8 mg pretreatment was followed by four subsequent 4-mg oral doses administered every 4 hours after chemotherapy.

The initial clinical trials with cisplatin that tested aprepitant in combination with dexamethasone and a 5-HT<sub>3</sub> serotonin receptor antagonist administered dexamethasone at a reduced dose of 12 mg on the day of chemotherapy.<sup>33-35</sup> In the trials in patients receiving cisplatin, dexamethasone was also administered at a reduced dosage of 8 mg once daily on days 2 and 3.<sup>33,34</sup> This was done to make the

**Table 8.** Dose and Schedule of Antiemetics to Prevent Emesis Induced by Antineoplastic Therapy of High Emetic Risk

Antiemetics for Intravenous Antineoplastic Therapy of High Emetic Risk	Single Dose Administered Before Chemotherapy	Single Dose Administered Daily
5-HT <sub>3</sub> serotonin receptor antagonists		
Dolasetron	Oral: 100 mg IV: 100 mg or 1.8 mg/kg	
Granisetron	Oral: 2 mg IV: 1 mg or 0.01 mg/kg	
Ondansetron	Oral: 24 mg IV: 8 mg or 0.15 mg/kg	
Palonosetron	IV: 0.25 mg	
Tropisetron	Oral or IV: 5 mg	
Dexamethasone	Oral: 12 mg (with aprepitant) Oral: 20 mg	Oral: 8 mg days 2, 3
Aprepitant	Oral: 125 mg	Oral: 80 mg days 2, 3

Abbreviations: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3; IV, intravenous.

**Table 9.** Dose and Schedule of Antiemetics to Prevent Emesis Induced by Antineoplastic Therapy of Moderate Emetic Risk

Antiemetics for Intravenous Antineoplastic Therapy of Moderate Emetic Risk	Single Dose Administered Before Chemotherapy	Single Dose Administered Daily
5-HT <sub>3</sub> serotonin receptor antagonists		
Dolasetron	Oral: 100 mg IV: 100 mg or 1.8 mg/kg	
Granisetron	Oral: 2 mg IV: 1 mg or 0.01 mg/kg	
Ondansetron	Oral: 16 mg (8 mg twice daily) IV: 8 mg or 0.15 mg/kg	
Palonosetron	IV: 0.25 mg Oral: 5 mg	
Tropisetron	IV: 5 mg	
Dexamethasone	IV: 8 mg Oral: 12 mg (with aprepitant)	Oral: 8 mg days 2, 3
Aprepitant*	Oral: 125 mg	Oral: 80 mg days 2, 3

Abbreviations: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3; IV, intravenous.  
\*For patients receiving a combination of an anthracycline and cyclophosphamide.

exposure to dexamethasone comparable on the standard and intervention arms of the trial. In volunteers, aprepitant increases the exposure (area under the curve) of dexamethasone because it acts as a moderate inhibitor of CYP3A4, and corticosteroids are a CYP3A4 substrate.<sup>36</sup> Aprepitant is discussed below.

*c. NK<sub>1</sub> Receptor Antagonists (note: this topic is new to the guideline).*

**Aprepitant.** NK<sub>1</sub> receptors, the binding site of the tachykinin substance P, are found in the brainstem emetic center and in the GI tract. Administering substance P to animals causes emesis. Likewise, pharmacologic agents that potently and specifically block this receptor subtype prevent emesis caused by virtually all experimental emetic stimuli (including cisplatin). Aprepitant is the first agent of this class available for general use.

After an extensive phase II controlled clinical trial program,<sup>37,38</sup> three phase III trials were undertaken in patients with cancer receiving chemotherapy of high (cisplatin) and moderate (anthracycline and cyclophosphamide) emetic risk. The primary study end point for all three studies was the documentation of no emetic episodes and no rescue therapy administered for the 120-hour period after chemotherapy. For the two identical trials in cisplatin-treated patients,<sup>33,34</sup> results in 1,043 patients have been reported from a pooled analysis by Warr et al.<sup>35</sup> Overall, vomiting prevention was improved by 20% ( $P < .001$ ; RR = 1.418; 95% CI, 1.275 to 1.579) for the 5-day period after cisplatin with the three-drug regimen of aprepitant, ondansetron, and dexamethasone (523 patients across the two trials) over the standard combination of ondansetron and dexamethasone alone (520 patients across the two trials). A 13% improvement in the prevention of acute emesis (RR = 1.177; 95% CI, 1.106 to 1.253), and a 21% improvement in the delayed phase (24 to 120 hours; RR = 1.409; 95% CI, 1.275 to 1.556) was seen as well ( $P < .001$  in both cases). There were no significant differences in any treatment-related adverse effect comparing the aprepitant-treated patients with controls in these studies.

An update of the Warr et al<sup>8</sup> pooled analysis, completed by the Cancer Care Ontario Program in Evidence-Based Care, reported a significant difference between groups (732 patients in the aprepitant group and 733 patients in the standard treatment group) in favor of the aprepitant-containing regimen (RR = 0.61; 95% CI, 0.54 to 0.69;  $P = .00001$ ). This represents a 20% absolute risk difference in overall

complete response in favor of the aprepitant group versus standard antiemetic therapy.<sup>8</sup> This corresponds to a number needed to treat of five (95% CI, four to six). The Cancer Care Ontario meta-analysis added two phase II/III trials to the two phase III trials included in the pooled analysis by Warr et al.<sup>8</sup> The conclusions of the systematic review of three trials conducted by Dando and Perry were consistent with these analyses, with a greater proportion of overall complete responses observed in the aprepitant arms of the trials (63% to 73% v 43% to 52%;  $P < .01$  for all comparisons).<sup>3</sup>

The effectiveness of aprepitant combined with ondansetron and dexamethasone day 1 and aprepitant alone days 2 and 3 was compared with ondansetron and dexamethasone day 1 and ondansetron alone days 2 and 3 in 857 assessable women with breast cancer receiving the combination of an anthracycline and cyclophosphamide in a randomized, placebo-controlled study.<sup>39</sup> Overall, vomiting prevention was improved by 9% ( $P = .015$ ) for the 5-day period after chemotherapy with the three-drug regimen of aprepitant, ondansetron, and dexamethasone, over the standard combination of ondansetron and dexamethasone alone. There were no significant differences in any treatment-related adverse effect comparing the aprepitant-treated patients with controls in these women. Control was maintained in those individuals who received multiple cycles of chemotherapy as well.<sup>14</sup>

Because aprepitant is a moderate inhibitor of CYP3A4, the metabolism of corticosteroids, which are 3A4 substrates, is affected in normal volunteers.<sup>36</sup> To ensure comparable exposures to dexamethasone administered as an antiemetic in both the standard and aprepitant study arms in the pivotal trials of aprepitant, the doses of dexamethasone were lowered from 20 to 12 mg on day 1 and from 16 to 8 mg on days 2 and 3. The effect on corticosteroid metabolism is greater for orally administered corticosteroids as well. The Panel cautions that the recommendation to use a lower dose of dexamethasone when administered *as an antiemetic* with aprepitant does not apply to the use of prednisone, dexamethasone, or any corticosteroid when administered *as an anticancer therapy* (ie, as part of cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP] or cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy regimens). Because aprepitant produces moderate inhibition of CYP3A4 in healthy volunteers, the concomitant

administration of aprepitant with chemotherapy agents such as cyclophosphamide and docetaxel (which in part are cleared by CYP3A4) theoretically could decrease the clearance of these drugs, resulting in prolonged exposure and toxicity, or in the case of cyclophosphamide, decreased exposure to its active metabolite. There has been no evidence in patients with cancer receiving standard doses and schedules of aprepitant with chemotherapy that these theoretical issues have any clinical sequelae. Among 857 patients who received cyclophosphamide, there was no difference in adverse effects when individuals receiving aprepitant were compared with those receiving placebo.<sup>39</sup> The incidence of febrile neutropenia was identical in aprepitant- and placebo-treated patients, suggesting that the exposure to the antineoplastic agents was comparable.<sup>39</sup> In patients with cancer receiving docetaxel, aprepitant had no clinically significant effect on docetaxel pharmacokinetics or toxicity.<sup>40</sup> In another study, although aprepitant reduced the exposure to the active metabolite of cyclophosphamide by 5%, inhibitory concentrations remained in the therapeutic range in the presence of aprepitant in a human liver microsome system.<sup>41</sup>

*i. Drug dose and schedule. Current recommendation.* Only the established dose and schedule of aprepitant should be used.

## **2. Antiemetic Agents: Lower Therapeutic Index—Metoclopramide, Butyrophenones, Phenothiazines, and Cannabinoids**

*Current recommendation.* For persons receiving chemotherapy of high emetic risk, there is no group of patients for whom agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT<sub>3</sub> serotonin receptor antagonists, NK<sub>1</sub> receptor antagonists, and dexamethasone.

*2006 literature update and discussion.* No relevant studies were identified from the review of the literature conducted for the update for antiemetic agents of lower therapeutic index, including metoclopramide, butyrophenones, phenothiazines, and cannabinoids. Of note, however, *the Panel's consensus was that, to prevent vomiting caused by chemotherapy of high or moderate emetic risk, there is no group of patients for whom metoclopramide, phenothiazines, butyrophenones, and cannabinoids are appropriate as first-choice antiemetics.* These agents should be reserved for patients intolerant of or refractory to 5-HT<sub>3</sub> serotonin receptor antagonists, dexamethasone, and aprepitant.

## **3. Antiemetic Agents: Adjunctive Drugs (benzodiazepines [lorazepam, alprazolam] and antihistamines [diphenhydramine])**

*Current recommendation.* Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs, but are not recommended as single agents. There is no change from the original guideline.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for the update for adjunctive drugs.

## **4. Antiemetic Agents: Combinations of Antiemetics**

*Current recommendation.* It is recommended that 5-HT<sub>3</sub> serotonin receptor antagonists be administered with dexamethasone and aprepitant in patients receiving chemotherapy of high emetic risk and in patients receiving an anthracycline in combination with cyclophosphamide (eg, AC). A 5-HT<sub>3</sub> serotonin receptor antagonist combined with dexamethasone should be used in patients receiving agents of moderate emetic risk other than AC.

*2006 literature update and discussion.* Among the antiemetic agents listed in the highest therapeutic index category, the combination of a 5-HT<sub>3</sub> serotonin receptor antagonist, dexamethasone, and aprepitant yields the greatest antiemetic protection in multicenter, randomized studies designed with sufficient numbers of patients to estimate precisely treatment effects with chemotherapy of high emetic risk and in patients receiving AC chemotherapy.<sup>33,34,39</sup> For all other situations in which 5-HT<sub>3</sub> serotonin receptor antagonist antiemetics are indicated for the prevention of acute emesis, we continue to recommend that dexamethasone be administered in addition.

## **5. Recommendations for Specific Emetic Risk Categories**

In creating antiemetic guideline recommendations, the primary determinant for choice of preventative therapy is the intrinsic emetic risk of the chemotherapy administered. The four emetic-risk categories established by the recent MASCC consensus conference were employed for this set of updated guideline recommendations (Tables 5 and 6).<sup>12</sup> Cross referencing for each antineoplastic agent in the current guideline to the four risk categories included in the 1999 version is listed in Table 6. Treatment recommendations refer to intravenously administered antineoplastic agents. Emetic risk categories used in the 2006 guideline are presented in Tables 5 and 6 and as follows.

*a. High (> 90%) Emetic Risk (includes agents from High: Cisplatin and High: Noncisplatin Emetic Risk categories in the 1999 Guideline).*

*Current recommendation.* The three-drug combination of a 5-HT<sub>3</sub> serotonin receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy of high emetic risk.

*2006 literature update and discussion.* The literature amply documents the high incidence of emesis with cisplatin.<sup>26,42,43</sup> These data are valuable in antiemetic studies for several reasons: cisplatin is useful in oncology, cisplatin causes emesis in all patients (> 99% risk without active antiemetics), and cisplatin provides a model for antiemetic testing. Trials to date show that, if an antiemetic is useful in preventing cisplatin-induced emesis, it will be useful with other chemotherapy drugs as well.<sup>44</sup> This fact is the basis of the Update Committee's recommendation for the use of the same antiemetic regimen used for cisplatin with all other agents of high emetic risk without clinical trial data testing the regimen specifically with each chemotherapeutic agent. The risk of emesis with cisplatin is universal. This observation has placed cisplatin at the top of all classification schemes. Treatment recommendations for cisplatin are independent of dose or infusion length.

Placebo-controlled trials in 1,053 randomly assigned patients have shown the no acute emesis and no rescue rate to be 86% after high-dose cisplatin using the recommended three-drug regimen.<sup>33,34</sup> Other agents with high emetic risk (> 90% frequency of emesis in the absence of antiemetic prophylaxis) include mechlorethamine, streptozotocin, carmustine, dacarbazine, and cyclophosphamide (> 1,500 mg/m<sup>2</sup>), and dactinomycin. For the reason cited above, although formal trials with aprepitant combined with a 5-HT<sub>3</sub> serotonin receptor antagonist and dexamethasone have not been reported for all high emetic risk agents, the Update Committee recommends this three-drug antiemetic combination to prevent acute emesis with these drugs as well as cisplatin.

*b. Moderate Emetic Risk (includes agents from High: Noncisplatin Emetic Risk category in the 1999 Guideline).*

*Current recommendation.* The three-drug combination of a 5-HT<sub>3</sub> receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving an AC regimen. For patients receiving other chemotherapy of moderate emetic risk, we continue to recommend the two-drug combination of a 5-HT<sub>3</sub> receptor serotonin antagonist and dexamethasone.

*2006 literature update and discussion.* The emetic risk for cyclophosphamide is well established.<sup>45</sup> Overall, the risk of emesis in this category (Tables 5, 6, and 7) is greater than 30% and less than that seen with cisplatin. The Update Committee recommends that the 1999 recommendation remain unchanged for patients receiving chemotherapy of moderate emetic risk, with the exception of patients receiving AC. During the last several years there has been growing appreciation that women receiving a combination of anthracycline plus cyclophosphamide are at high risk to experience emesis. A recent trial reported by Warr et al<sup>39</sup> documented a significantly higher rate of complete response during 5 days (the primary study end point) with aprepitant combined with ondansetron and dexamethasone compared with ondansetron and dexamethasone alone in 866 patients with breast cancer receiving cyclophosphamide combined with doxorubicin or epirubicin. The three-drug regimen was numerically superior to ondansetron and dexamethasone for the prevention of acute emesis. In analyses of the primary trial end point of overall complete response, adjusted for treatment group, investigator group, and patient age category, a greater proportion of patients who received aprepitant reported a complete response during both the acute phase (76% v 69%;  $P = .034$ ) and the delayed phase (55% v 49%;  $P = .064$ ). The Panel recommends the three-drug antiemetic regimen of a 5-HT<sub>3</sub> serotonin receptor antagonist, dexamethasone, and aprepitant tested by Warr et al<sup>39</sup> for any chemotherapeutic regimen that includes cyclophosphamide alone (750 to 1,500 mg/m<sup>2</sup>) or in combination with an anthracycline (doses of 500 to 1,500 mg/m<sup>2</sup>; the doses received by the patients in the study). The use of this three-drug antiemetic regimen, has not been tested specifically in patients receiving the CHOP chemotherapy regimen. The Panel further recommends that the dosages and schedules of any corticosteroids that are part of the treatment regimen (for example, the prednisone in CHOP) *not be reduced* due to the concomitant use of aprepitant. It may be appropriate to reduce the dose of dexamethasone administered as part of the antiemetic regimen based on patient comorbidities and tolerance.

*c. Low (10% to 30%) Emetic Risk (includes agents from Intermediate Emetic Risk category in the 1999 Guideline)*

*Current recommendation.* Dexamethasone 8 mg is suggested for patients treated with agents of low emetic risk.

*2006 literature update and discussion.* Tables 5, 6, and 7 list chemotherapy agents in this category. Without treatment, many patients, but not the majority, have emesis. The risk of emesis is estimated to be 10% to 30% for drugs in this group. The first few agents in this list were considered by some Update Committee members to be in the moderate emetic risk category. The lower few were listed in the minimal-risk group by some as well. Evidence for emetic risk is often found as part of phase I and II chemotherapeutic trials for the newer agents in this category, rather than as part of comparative antiemetic studies. There are no trials specifically addressing the optimal antiemetics for chemotherapies of low emetic risk.

*d. Minimal (<10%) Emetic Risk (includes agents from Low Emetic Risk category in the 1999 Guideline).*

*Current recommendation.* No change from the original guideline. It is suggested that for patients treated with agents of minimal emetic risk, no antiemetic be routinely administered before chemotherapy.

*2006 literature update and discussion.* Few antiemetic studies were found that included patients receiving these chemotherapeutic agents, which are listed in Tables 5, 6, and 7. With small risk (estimated < 10% for most agents), it is understandable that trials were not conducted. Some of the agents listed at the top of this category would be placed in the low-risk category by some members of the Update Committee. As in all of the categories, individual patients, especially those with poor emetic control during prior drug administration, may require antiemetics pretreatment. Use of a single dose of dexamethasone 8 mg, as-needed prescribing of oral metoclopramide, or a phenothiazine is common.

*e. Combination Chemotherapy.*

*Current recommendation.* When combination chemotherapy is administered, the patient should be administered antiemetics appropriate for the component chemotherapeutic agent of greatest emetic risk. There is no change from the original guideline.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for this topic.

*f. Multiple Consecutive Days of Chemotherapy.*

*Current recommendation.* Antiemetics appropriate for the risk class of the chemotherapy, as outlined above, should be administered for each day of the chemotherapy. There is no change from the original guideline.

*2006 literature update.* No relevant studies were identified from the review of literature conducted for multiple consecutive days of chemotherapy.

## **B. VOMITING OCCURRING 24 OR MORE HOURS AFTER CHEMOTHERAPY (DELAYED EMESIS)**

### **1. Chemotherapeutic Agents**

Delayed emesis initially was described in patients receiving cisplatin.<sup>46-49</sup> Only recently has the problem been described in patients administered other chemotherapies.<sup>50-52</sup> Given that the risk of delayed emesis in patients receiving most chemotherapy drugs has not been studied formally, the recommendations listed in Tables 8, 9, and 10 largely represent a consensus of Panel members and other guideline groups. Any emesis during the initial 24 hours after chemotherapy predicts a higher likelihood of emesis persisting or starting more than 24 hours after antineoplastic therapy.<sup>46,47,53,54</sup>

### **2. Antiemetics to Prevent Emesis Occurring 24 or More Hours After Chemotherapy**

*a. Dexamethasone.* Dexamethasone, used alone and in combination, is the most widely studied drug for the prevention of emesis occurring 24 or more hours after chemotherapy.<sup>33,34,48,52,54-56</sup> Factors favoring the use of dexamethasone are its proven benefit in clinical trials, widespread availability in oral form, low cost, and incremental effectiveness in patients receiving chemotherapies of high emetic risk. Given that dexamethasone typically is administered as an antiemetic for 2 to 4 days, adrenal insufficiency has not been described. Clinically significant hyperglycemia and insomnia occur rarely. Dexamethasone dose and schedule have not been determined by formal testing in this setting. The Update Panel agreed that dexamethasone should be part

of any regimen for delayed emesis after cisplatin, unless there is an absolute contraindication to its use. However, in a recent trial of aprepitant in patients receiving AC, dexamethasone was not used in either the aprepitant or control regimen administered on days 2 and 3 after chemotherapy.<sup>39</sup>

*b. Aprepitant.* Initial trials testing NK<sub>1</sub> receptor antagonists suggested that this class of agents was likely to be effective in preventing delayed emesis.<sup>57</sup> The subsequent experience with aprepitant used alone to prevent delayed emesis in controlled phase II trials confirmed that this suspicion was correct in patients receiving cisplatin.<sup>58</sup> In placebo-controlled phase III trials of 1,053 randomly assigned patients receiving cisplatin, 72% of individuals receiving the combination of aprepitant and dexamethasone had no delayed vomiting or rescue compared with 51% receiving dexamethasone alone.<sup>33,34</sup> In 866 patients receiving the combination of AC, 55% of patients receiving aprepitant 80 mg once daily had no delayed emesis and no rescue as opposed to 49% receiving ondansetron 8 mg twice daily ( $P = .064$ ).<sup>39</sup>

*c. Metoclopramide and 5-HT<sub>3</sub> Serotonin Receptor Antagonists.* Several trials have reported efficacy for oral metoclopramide administered in combination with dexamethasone.<sup>47,48,54,59-62</sup> Doses vary between 20 and 40 mg (or 0.5 mg/kg) administered two to four times per day for 3 to 4 days. This agent is generally well tolerated, with few acute dystonic reactions in adults. Akathisia (restlessness) may occur.

Studies conflict on the effectiveness of 5-HT<sub>3</sub> serotonin antagonists for the prevention of emesis 24 or more hours after chemotherapy. Ondansetron and granisetron have been administered either singly<sup>50,63-69</sup> or in combination with dexamethasone.<sup>49,53,55,56,59,62,70</sup> One randomized study demonstrated that ondansetron prevented delayed emesis in patients receiving chemotherapy of moderate emetic risk.<sup>50</sup> The Cancer Care Ontario meta-analysis of eight randomized, placebo-controlled trials (2,966 total patients) evaluating 5-HT<sub>3</sub> serotonin antagonist use beyond 24 hours after chemotherapy showed a difference between groups (RR = 0.92; 95% CI, 0.85 to 0.98;  $P = .016$ ). This translates into an absolute improvement in complete response rate of 5%.<sup>4</sup>

Among patients in similar risk groups, single intravenous doses of palonosetron were compared with single intravenous doses of ondansetron<sup>28</sup> and dolasetron<sup>29</sup> for their ability to prevent emesis more than 24 hours following chemotherapy. In the latter study, palonosetron was superior to dolasetron.<sup>29</sup> Complete response during the period from 24 to 120 hours after chemotherapy was improved over ondansetron ( $P < .001$ ) with a single intravenous dose of palonosetron 0.25 mg administered before chemotherapy.<sup>28</sup> These data suggest that the use of palonosetron before chemotherapy improves the control of delayed vomiting better than single doses of ondansetron and dolasetron. Although numerically better, palonosetron was not superior to ondansetron in preventing delayed emesis after cisplatin.<sup>71</sup> The majority of patients in this trial received dexamethasone as well. The Update Committee recommends aprepitant and dexamethasone when it is necessary to prevent emesis occurring 24 or more hours after chemotherapy, based on the effectiveness of this regimen in patients receiving cisplatin. One trial has studied aprepitant to prevent emesis in patients receiving chemotherapy of moderate emetic risk. In this trial in women receiving the combination of AC, dexamethasone was only administered pretreatment and not administered daily to prevent emesis occurring more than 24 hours after chemotherapy. Here, 55% of individuals receiving aprepitant 80 mg once daily had no delayed

emesis and no rescue as opposed to 49% receiving ondansetron 8 mg twice daily ( $P = .064$ ).<sup>39</sup>

### 3. Recommendations to Prevent Emesis Occurring 24 or More Hours After Chemotherapy

*a. High Emetic Risk (includes agents from High: Cisplatin and High: Noncisplatin Emetic Risk categories in the 1999 Guideline)*

*Current recommendation.* In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended for the prevention of delayed emesis. The Update Committee no longer recommends the combination of a 5-HT<sub>3</sub> serotonin receptor antagonist and dexamethasone for the prevention of delayed emesis after chemotherapeutic agents of high emetic risk.

*2006 literature update and discussion.* Two randomized, placebo-controlled trials have demonstrated that the combination of aprepitant and dexamethasone is superior to dexamethasone alone for this indication.<sup>33,34</sup> The optimal prophylactic regimen for preventing delayed emesis with high emetic risk drugs other than cisplatin has not been studied to date.

The Update Committee no longer recommends the combination of a 5-HT<sub>3</sub> serotonin receptor antagonist and dexamethasone for the prevention of delayed emesis after chemotherapeutic agents of high emetic risk. A detailed analysis of clinical trial data for these patients has failed to demonstrate that the combination of a 5-HT<sub>3</sub> serotonin receptor antagonist plus dexamethasone is superior to dexamethasone alone.<sup>72-74</sup> In addition, a recent trial reported in abstract form found that a combination of aprepitant and dexamethasone was superior to ondansetron and dexamethasone in the prevention of cisplatin-induced delayed emesis.<sup>17</sup> Based on this information and the demonstrated effectiveness of aprepitant and dexamethasone for this indication, both the MASCC Consensus Conference<sup>13</sup> and the Update Committee no longer recommend that a 5-HT<sub>3</sub> antagonist plus dexamethasone be used to prevent delayed emesis after chemotherapy of high emetic risk.

*b. Moderate Emetic Risk (includes agents from High: Noncisplatin Emetic Risk category in the 1999 Guideline)*

*Current recommendation.* In patients receiving AC, aprepitant as a single agent is recommended. For all other chemotherapies of moderate emetic risk, single-agent dexamethasone or a 5-HT<sub>3</sub> serotonin receptor antagonist is suggested for the prevention of delayed emesis.

*2006 literature update and discussion.* Among patients receiving AC plus carboplatin, the incidence of delayed emesis varies from 20% to 30% in individuals not administered prophylactic antiemetics for delayed emesis.<sup>75</sup> Use of dexamethasone as part of the acute emesis regimen was associated with a lower incidence of delayed emesis. The majority of Update Committee members recommended that prophylactic antiemetics be administered with this degree of risk, but data to support this recommendation are sparse. In the absence of trial data, Update Committee members recommended using the same dosages as administered for cisplatin-induced delayed emesis (High Emetic Risk discussed above; Tables 9 and 10). Aprepitant alone is recommended for the prevention of delayed emesis in patients receiving AC chemotherapy. One randomized, placebo-controlled trial studying 857 patients receiving the combination of AC has demonstrated the superiority of a three-drug aprepitant-containing regimen over a two-drug ondansetron plus dexamethasone regimen for the prevention of emesis more

**Table 10.** Drug Regimens for the Prevention of Emesis Selected by the Emetic Risk Category of the Radiation Administered

Radiation Emetic Risk	Irradiated Area	Recommended Antiemetics
High (> 90%)	Total body	Prophylaxis with 5-HT <sub>3</sub> serotonin receptor antagonist ± dexamethasone with each fraction and 24 hours after
Moderate (60% to 90%)	Upper abdomen	Prophylaxis with 5-HT <sub>3</sub> serotonin receptor antagonist
Low (30% to 60%)	Lower thorax and pelvis Cranium (radiosurgery) and craniospinal	Prophylaxis or rescue with 5-HT <sub>3</sub> serotonin receptor antagonist
Minimal (< 30%)	Head and neck, extremities, cranium, breast	Rescue with dopamine receptor antagonist or 5-HT <sub>3</sub> serotonin receptor antagonist

Abbreviation: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3.

than the 5 days after chemotherapy.<sup>39</sup> The three-drug regimen was numerically but not significantly superior to the two-drug regimen during the period from 25 to 120 hours after chemotherapy.

*c. Low and Minimal Emetic Risk (includes agents from Intermediate and Low Emetic Risk categories in the 1999 guideline)*

*Current recommendation.* No change from the original guideline. No routine preventive antiemetics for delayed emesis are indicated for patients receiving chemotherapeutic agents of low or minimal emetic risk.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for delayed emesis with chemotherapeutic agents of low or minimal emetic risk.

### C. SPECIAL EMETIC PROBLEMS

#### 1. Anticipatory Emesis

Anticipatory or conditioned emesis occurs in patients who have had poor control of vomiting with prior chemotherapy.<sup>62,76-85</sup> A history of motion sickness predisposes patients to anticipatory emesis.<sup>86,87</sup>

##### a. Prevention of Anticipatory Emesis

*Current recommendation.* No change from original guideline. Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens must be used with the initial chemotherapy, rather than after assessing the patient's emetic response with less effective treatment.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for anticipatory emesis.

##### b. Treatment of Anticipatory Emesis

*Current recommendation.* No change from original guideline. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested.

*2006 literature update.* No relevant studies were identified from the review of literature conducted for the treatment of anticipatory emesis. Because of their amnestic and antianxiety effects, alprazolam and lorazepam have been used to treat and prevent anticipatory symptoms. Although many Update Committee members recommend lorazepam and alprazolam, there are no prospective trials to establish their effectiveness in this setting.

#### 2. Emesis in Pediatric Oncology Patients

*Current recommendation.* The combination of a 5-HT<sub>3</sub> antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Due to variation of pharmacokinetic parameters in children, higher weight-

based doses of 5-HT<sub>3</sub> antagonists than those used in adults may be required for antiemetic protection.

*2006 literature update and discussion.* Antiemetic research in pediatric populations continues to be hampered by small patient populations and by the resulting tendency to include chemotherapeutic agents of different emetogenic levels in the same study. However, a growing body of literature, including two randomized trials and three dose-ranging studies, suggests that, similar to adults, a 5-HT<sub>3</sub> antagonist with<sup>88,89</sup> or without<sup>90-92</sup> a corticosteroid provides antiemetic protection for patients receiving moderately emetogenic as well as highly emetogenic chemotherapy. Of note, due to wider interpatient variations in metabolism and clearance<sup>93</sup> or more rapid clearance in younger pediatric patients,<sup>91,92</sup> standard adult doses of 5-HT<sub>3</sub> antagonists may not be sufficient to provide consistent antiemetic protection in children.<sup>94</sup> For granisetron, for example, an intravenous dose of 40 µg/kg may be superior to lower doses.<sup>95</sup>

Few reports address the incidence and treatment of delayed emesis in children receiving cancer chemotherapy.<sup>96</sup> Dopamine antagonists, especially when administered over several consecutive days, cause a high incidence of dystonic reactions and are not a good choice for general multiple-day use in the pediatric patients.<sup>96,97</sup>

#### 3. High-Dose Chemotherapy

*Current recommendation.* No change from original guideline. A 5-HT<sub>3</sub> serotonin receptor antagonist antiemetic combined with a corticosteroid is suggested. The Update Committee encourages exploring the addition of aprepitant to the antiemetic regimens used for patients receiving high-dose chemotherapy.

*2006 literature update.* No relevant studies were identified from the review of the literature conducted for high-dose chemotherapy. Based on the emetic risk posed by high-dose chemotherapy, the Update Committee urges that the use of aprepitant be considered. However, there is no data specifically studying aprepitant in patients receiving high-dose chemotherapy. Although there have been no clinically significant sequelae of using aprepitant with corticosteroids, chemotherapy, or any other drug in the trials of aprepitant in persons with cancer, there is a theoretical possibility for a drug interaction because aprepitant has been shown to moderately inhibit CYP3A4 in normal volunteers.

#### 4. Vomiting and Nausea Despite Recommended Prophylaxis

*Current recommendation.* No change from original guideline. The Update Committee suggests that clinicians (1) conduct a careful

evaluation of risk, antiemetic, chemotherapy, tumor, and concurrent disease, and medication factors; (2) ascertain that the best regimen is being administered for the emetic setting; (3) consider adding an lorazepam or alprazolam to the regimen; and (4) consider substituting a high-dose intravenous metoclopramide for the 5-HT<sub>3</sub> antagonist or adding a dopamine antagonist to the regimen.

**2006 literature update.** No relevant studies were identified from the review of the literature conducted for vomiting and nausea despite recommended prophylaxis.

## II. RADIATION-INDUCED EMESIS

### A. RISK FACTORS FOR RADIATION-INDUCED EMESIS

The risk of emesis with radiotherapy varies with the treatment administered.<sup>98-107</sup> Only a minority of patients receives radiation therapy of high emetic risk, and, in that group of patients, the problem can be difficult to prevent or control. Controversy exists, caused by a lack of systematic study, concerning definitions of emetic risk groups. As with chemotherapy-induced emesis, it is the identification of these risk groups that indicates whether antiemetic therapy should be administered routinely on a preventative basis, or whether antiemetics should be reserved for treatment as needed by individual patients. The radiation oncology literature indicates that treatment field is one of the major determinants of emetic risk. More difficult to define, but also important considerations for risk, are the dose of radiotherapy administered per fraction and the pattern of fractionation. Using available data and clinical experience, the Update Committee reached consensus on definitions of four radiotherapy-induced emesis risk groups (Table 10). This represents a modification from the 1999 guideline, which defined three radiotherapy-induced emesis risk groups.<sup>18</sup>

### B. RECOMMENDATIONS FOR RADIATION-INDUCED EMESIS

#### 1. High Risk: Total-Body Irradiation

**Current recommendation.** The Update Committee suggests administration of a 5-HT<sub>3</sub> serotonin receptor antagonist with or without a corticosteroid before each fraction and for at least 24 hours after. There is no change from the original guideline.

**2006 literature update.** No relevant studies were identified from the review of the literature conducted for radiation-induced emesis.

#### 2. Moderate Emetic Risk: Upper Abdomen (intermediate risk) Hemibody Irradiation, Upper Abdomen, Abdominal-Pelvic, Mantle, Craniospinal Irradiation, and Cranial Radiosurgery

**Current recommendation.** The Update Committee recommends a 5-HT<sub>3</sub> serotonin receptor antagonist before each fraction.

**2006 literature update and discussion.** Evidence suggests that preventative treatment is better than intervention on an as-needed basis in this group (Table 10), and that 5-HT<sub>3</sub> serotonin receptor antagonists are more effective than metoclopramide or phenothiazines.<sup>100,108</sup> There may be smaller differences between these agents in intermediate-risk settings than in higher-risk settings, and therefore dopamine receptor antagonists may be more appropriate, particularly in patients receiving craniospinal radiotherapy or radiotherapy to the lower-half of the body, where there is somewhat less risk of emesis.<sup>109</sup> There is also some evidence to suggest that in fractionated radiotherapy, the efficacy of 5-HT<sub>3</sub> antagonists may decrease after the first week of treatment,<sup>110</sup> making it difficult to suggest the optimal duration of prophylactic treatment.

#### 3. Low Emetic Risk: Lower Thorax, Cranium (radiosurgery), and Craniospinal

**Current recommendation.** The Update Committee recommends a 5-HT<sub>3</sub> serotonin receptor antagonist before each fraction. There is no change from original guideline.

**2006 literature update.** No relevant studies were identified from the review of the literature conducted for low emetic risk radiation, including lower thorax, cranial, or craniospinal radiation.

#### 4. Minimal Emetic Risk: Radiation of Breast, Head and Neck, Cranium, and Extremities (low emetic risk)

**Current recommendation.** The Update Committee suggests that treatment be administered on an as-needed basis. Dopamine or 5-HT<sub>3</sub> serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day. There is no change from original guideline.

**2006 literature update.** No relevant studies were identified from the review of the literature conducted for minimal emetic risk associated with radiation to the breast, head and neck, cranium, or extremities. The incidence of emesis in this patient group, as defined in Table 10, is less than 30%.

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### **Appendix 1**

*2006 ASCO Antiemetic Guideline Update Expert Panel, Update Panel Member Institutions:* Mark G. Kris, MD, *Chair* Memorial Sloan-Kettering Cancer Center; Richard J. Gralla, MD, New York Lung Cancer Alliance; Maurice J. Chesney, Patient Representative; Lawrence W. Chinnery, Patient Representative; Rebecca Clark-Snow, RN, BSN, OCN, University of Kansas Cancer Center; Petra Feyer, MD, Viviventes Clinics Beniu-Needcoellin; Steven M. Grunberg, MD, University of Vermont; Paul J. Hesketh, MD, Caritas St Elizabeth's Medical Center; Jim M. Koeller, MS, University of Texas Health Science Center; and Gary R. Morrow, PhD, MS, University of Rochester Cancer Center.

### **Appendix 2**

For the 2006 update, a methodology similar to that applied in the original ASCO practice guidelines for antiemetics was used. Pertinent information published from 1998 through February 2006 was reviewed. The MEDLINE database (National Library of Medicine, Bethesda, MD) was searched to identify relevant information from the published literature for this update. A series of searches was conducted using the medical subject headings or text words "vomiting," "nausea," "neoplasms," "cancer," "tumor," "tumor," and "malignant." These terms were combined with a range of medical subject headings and text words representing available antiemetics agents: "antiemetics," "5-HT3 antagonist," "serotonin antagonist," "dolasetron," "granisetron," "ondansetron," "tropisetron," "dexamethasone," "methylprednisone," "metoclopramide," "prochlorperazine," "aprepitant," "palonosetron," "L-754030," "L-758298," "substance P," "MK-869," and "receptors, neurokinin-1." Finally, these searches were combined serially with medical subject headings or text words corresponding to each of the major topical sections of the guideline, including, for example, "child" or "pediatric," "refractory" or "control," "radiotherapy" or "irradiation," and "bone marrow transplantation" or "high-dose chemotherapy."

Search results were limited to human studies and English-language articles. The Cochrane Library was searched with the phrase "antiemetic." Directed searches based on the bibliographies of primary articles were also performed. Finally, Update Committee members contributed articles from their personal collections. Specific Antiemetic Update Committee members were assigned to review the collected materials corresponding to the major sections of the guideline document.

### Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Mark G. Kris			Merck and Company (B); MGI Pharma (B); Sanofi-Aventis (B); GlaxoSmithKline (A)				Merck and Company (N/R)	
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## ERRATUM

The June 20, 2006, ASCO special article by Kris et al entitled, “American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006” (J Clin Oncol 24:2932-2947, 2006) contained errors.

In Section I, “Emesis Caused By Intravenously Administered Antineoplastic Agents,” the headings under Subsection A, “Vomiting Occurring 0 To 24 Hours After Therapy (Acute Emesis)” should have been numbered as follows:

1. Emetic Risk of Antineoplastic Agents: Emetic Risk Categories
2. Antiemetic Agents: Highest Therapeutic Index
3. Antiemetic Agents: Lower Therapeutic Index—Metoclopramide, Butyrophenones, Phenothiazines, and Cannabinoids
4. Antiemetic Agents: Adjunctive Drugs (benzodiazepines [lorazepam, alprazolam] and antihistamines [diphenhydramine])
5. Antiemetic Agents: Combinations of Antiemetics
6. Recommendations for Specific Emetic Risk Categories

In Table 7, under “Antiemetic Regimens and Schedules,” Dexamethasone was scheduled on days 1, 2 and 3 for “High” emetic risk, and should have been given on **days 1-4**. Also, Dexamethasone was scheduled on day 1 only for “Moderate” emetic risk, and should have been listed as **continuing on days 2 and 3 when aprepitant is not given**. The corrected table is reprinted below in its entirety.

Emetic Risk Category (incidence of emesis without antiemetics)	Antiemetic Regimens and Schedules
High (> 90%)	5-HT <sub>3</sub> serotonin receptor antagonist: day 1 Dexamethasone: days 1-4 Aprepitant: days 1, 2, 3
Moderate (30% to 90%)	5-HT <sub>3</sub> serotonin receptor antagonist: day 1 Dexamethasone: day 1 (2, 3)* (Aprepitant: days 1, 2, 3)†
Low (10% to 30%)	Dexamethasone: day 1
Minimal (< 10%)	Prescribe as needed (see text for details of agent selection)

Abbreviation: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3.  
\*May omit days 2 and 3 if aprepitant is given.  
†For patients receiving a combination of an anthracycline and cyclophosphamide.

In Table 8, under “Single Dose Administered Before Chemotherapy,” “Oral: 12 mg (with aprepitant)” and “Oral: 20 mg” were listed for Dexamethasone, while it should have read, “Oral: **12 mg**” only. Under “Single Dose Administered Daily,” “Oral: 8 mg days 2, 3” was listed for Dexamethasone, while it should have read, “Oral: 8 mg **days 2-4**.” Also, “Dexamethasone” should have been left-justified as a row heading. The corrected table is reprinted below in its entirety.

**Table 8.** Dose and Schedule of Antiemetics to Prevent Emesis Induced by Antineoplastic Therapy of High Emetic Risk

Antiemetics for Intravenous Antineoplastic Therapy of High Emetic Risk	Single Dose Administered Before Chemotherapy	Single Dose Administered Daily
5-HT <sub>3</sub> serotonin receptor antagonists		
Dolasetron	Oral: 100 mg IV: 100 mg or 1.8 mg/kg	
Granisetron	Oral: 2 mg IV: 1 mg or 0.01 mg/kg	
Ondansetron	Oral: 24 mg IV: 8 mg or 0.15 mg/kg	
Palonosetron	IV: 0.25 mg	
Tropisetron	Oral or IV: 5 mg	
Dexamethasone	Oral: 12 mg	Oral: 8 mg days 2-4
Aprepitant	Oral: 125 mg	Oral: 80 mg days 2, 3

Abbreviations: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3; IV, intravenous.

On page 2937, the second sentence of the last paragraph was given as: “In the trials in patients receiving cisplatin, dexamethasone was also administered at a reduced dosage of 8 mg once daily on days 2 and 3.<sup>33,34</sup>”

While it should have read:

“In the trials in patients receiving cisplatin, dexamethasone was also administered at a reduced dosage of 8 mg once daily on **days 2 to 4**.<sup>33,34</sup>”

In Table 9, under “Dexamethasone,” both 8 mg doses should have been listed as “**without aprepitant.**”

On page 2938, the second sentence of the second to last paragraph was given as: “Overall, vomiting prevention was improved by 9% ( $P = .015$ ) for the 5-day period after chemotherapy with the three-drug regimen of aprepitant, ondansetron, and dexamethasone, over the standard combination of ondansetron and dexamethasone alone.”

While it should have read:

“**Complete response** was improved by 9% ( $P = .015$ ) for the 5-day period after chemotherapy with the three-drug regimen of aprepitant, ondansetron, and dexamethasone, over the standard combination of ondansetron and dexamethasone alone.<sup>39</sup>”

Also on page 2938, the second to last sentence of the last paragraph was given as:

“The Panel cautions that the recommendation to use a lower dose of dexamethasone when administered *as an antiemetic* with aprepitant does not apply to the use of prednisone, dexamethasone, or any corticosteroid when administered *as an anticancer therapy* (ie, as part of cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP] or cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy regimens).”

While it should have read:

“The Panel cautions that the recommendation to use a lower dose of dexamethasone when administered *as an antiemetic* with aprepitant does not apply to the use of prednisone, dexamethasone, or any corticosteroid when administered *as an anticancer therapy* (ie, as part of cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]-**based** or **mechlorethamine, vincristine, procarbazine, and prednisone [MOPP]** chemotherapy regimens).”

The online version has been corrected in departure from the print.

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