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February 14, 2012

Re: Formal Request for Reconsideration of the National Coverage Determination for Aprepitant for Chemotherapy-Induced Emesis (110.18)

Dear Dr. Jacques:

This letter formally requests a reconsideration of the April 4, 2005 National Coverage Determination (NCD) concerning Aprepitant for Chemotherapy-Induced Emesis (110.18). Aprepitant is currently covered under the Oral Antiemetic Drug benefit category.

Since the initial Aprepitant NCD became effective April 4, 2005, the U.S. Food and Drug Administration (FDA) has expanded aprepitant's approved indications to include moderately emetogenic anticancer chemotherapy (MEC) agents. In addition, the emetogenic potential ratings of cancer chemotherapy medications were updated adding new anticancer medications and standards of care involving patients undergoing anticancer chemotherapy treatment have evolved. To provide the most appropriate care for Medicare patients receiving anticancer chemotherapy, it is necessary to consider incorporating these updated materials into the current Aprepitant NCD.

In this aprepitant NCD reconsideration, we request consideration of the following items as reasonable and necessary in the following patient populations and situations:

- Expand the use of aprepitant in combination with dexamethasone and a 5-HT3 antagonist to include the patient population receiving anticancer chemotherapeutic agents currently considered moderately emetogenic. MEC agents classified using the Hesketh emetogenic classification system or listed in at least two published evidence-based guidelines include alemtuzumab, azacitidine, bendamustine, carboplatin, clofarabine, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.
- Expand coverage of aprepitant in combination with dexamethasone and a 5-HT3 antagonist for use with future chemotherapy agents classified as highly emetogenic or moderately emetogenic using the Hesketh emetogenic classification system or listed in at least two published evidence-based guidelines.
- Expand the current NCD acceptable list of 5-HT3 antagonists for use with aprepitant and dexamethasone to include palonosetron.

- Allow use of therapeutically equivalent doses of any available 5-HT3 antagonist, dexamethasone, and aprepitant formulations (oral, transdermal, intravenous).
- Allow for oral dexamethasone taken by the patient at home during the time period of chemotherapy administration.
- Allow for the intravenous administration of dexamethasone in place of oral dexamethasone.
- Allow for aprepitant in combination with 5-HT3 antagonists in patients shown to be dexamethasone (corticosteroid) intolerant or if the physician wishes to avoid dexamethasone (corticosteroids) because the patient is a diabetic.

Application of Decision Memo Rationale

Within the Aprepitant for Chemotherapy-Induced Emesis (CAG-00248N) Decision Memo, it is mentioned that aprepitant received FDA approval September 27, 2002 for use in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC), including high-dose cisplatin. Furthermore, the Decision Memo defined the patient population for which the use of the oral antiemetic three drug combination of aprepitant, a 5-HT3 antagonist, and dexamethasone is reasonable and necessary as: 1.) Only those patients who are receiving anticancer chemotherapeutic agents defined as level 5 on Hesketh's classification system of acute emetogenicity of anticancer chemotherapeutic agents or 2.) Agents listed in the highest category of emetogenicity, regardless of dose, in two or more of the published clinical guidelines from NCCN, MASCC, ASHP, or ASCO. Although not cited within the Decision Memo, the Hesketh emetogenicity classification system is likely to have been based upon the 1997 Hesketh et al publication.[1] A 2011 update of the Hesketh emetogenicity classification system has been published.[2]

Aprepitant subsequently received a second FDA approval on October 28, 2005 for use in combination with other antiemetic agents for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC).[3] A discussion of the clinical support for this new FDA indication will follow. Applying the rationale used in the aforementioned Decision Memo, the use of the oral antiemetic three drug combination of aprepitant, a 5-HT3 antagonist, and dexamethasone is reasonable and necessary as 1.) In those patients who are receiving anticancer chemotherapeutic agents defined as moderately emetogenic using Hesketh's classification system of acute emetogenicity of anticancer chemotherapeutic agents or 2.) Agents listed in the moderate emetogenic category, regardless of dose, in two or more of the published clinical guidelines from NCCN, ASCO, and MASCC. ASHP antiemetic guidelines, not updated since the 1999 publication, have intentionally not been included in this document. As shown in the table below (highlighted in yellow), anticancer chemotherapeutic agents listed as moderately emetogenic in Hesketh 2011 or two or more published clinical guidelines include: alemtuzumab, azacitidine, bendamustine, carboplatin, clofarabine, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin. Therefore, these medications should be added to the list of anticancer chemotherapy agents covered by the Aprepitant NCD.

[1] Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997; 15: 103-109.

[2] Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity – state of the art. Support Care Cancer 2011; 19 (Suppl 1): S43-S47.

[3] Emend (aprepitant) package insert. Merck & Co., Inc. Whitehouse Station, NJ, 08889.

Moderately Emetogenic Anticancer Chemotherapy			
Hesketh 2011	**NCCN 2012**	**ASCO 2011**	**MASCC 2010**
	Aldesleukin > 12-15 million international units/m^2		
Alemtuzumab		Alemtuzumab	Alemtuzumab
	Amifostine > 300 mg/m^2		
	Arsenic Trioxide		
Azacitidine	Azacitidine	Azacitidine	Azacitidine
Bendamustine	Bendamustine	Bendamustine	Bendamustine
	Busulfan		
Carboplatin	Carboplatin	Carboplatin	Carboplatin
	Carmustine ≤ 250 mg/m^2		
	Cisplatin < 50 mg/m^2		
Clofarabine	Clofarabine	Clofarabine	Clofarabine
Cyclophosphamide < 1,500 mg/m^2	Cyclophosphamide < 1,500 mg/m^2	Cyclophosphamide < 1,500 mg/m^2	Cyclophosphamide < 1,500 mg/m^2
Cytarabine > 1 g/m^2	Cytarabine > 200 mg/m^2	Cytarabine > 1 g/m^2	Cytarabine > 1 g/m^2
	Dactinomycin		
Daunorubicin	Daunorubicin	Daunorubicin	Daunorubicin
Doxorubicin	Doxorubicin ≤ 60 mg/m^2	Doxorubicin	Doxorubicin
Epirubicin	Epirubicin ≤ 90 mg/m^2	Epirubicin	Epirubicin
Idarubicin	Idarubicin	Idarubicin	Idarubicin
Ifosfamide	Ifosfamide ≤ 10 g/m^2	Ifosfamide	Ifosfamide
	Interferon alfa ≥ 10 million international units/m^2		
Irinotecan	Irinotecan	Irinotecan	Irinotecan
	Melphalan		
	Methotrexate ≥ 250 mg/m^2		
Oxaliplatin	Oxaliplatin	Oxaliplatin	Oxaliplatin
	Temozolomide		

New Evidence to Support the Use of Aprepitant with MEC

1. Clinical Research and Evidence

Warr, Herrstedt, and Rapoport performed research demonstrating the benefit of adding aprepitant to ondansetron and dexamethasone to patients receiving MEC. Their research findings are summarized below. Warr et al performed a prospective, multicenter, randomized, double-blind, controlled trial to assess the efficacy and tolerability of ondansetron plus dexamethasone ± aprepitant in 857 assessable breast cancer patients naïve to emetogenic chemotherapy who were treated with cyclophosphamide ± doxorubicin or epirubicin.[4] The control regimen (ondansetron + dexamethasone) was given to 428 patients and the aprepitant regimen (ondansetron+ dexamethasone+ aprepitant) to 438 patients. The study medication schedule is shown in Table 1 in Appendix A. Treatment groups were similar with respect to baseline characteristics including race, sex, age, history of motion sickness, and history of vomiting during pregnancy. Overall complete response (CR) rate (defined as no vomiting and no use of rescue therapy during the 120 hours after the initiation of the first chemotherapy cycle) was greater with the aprepitant regimen than with the control regimen (50.8% versus 42.5%; P = .015). Using a Functional Living Index-Emesis questionnaire, more patients in the aprepitant group reported minimal or no impact of chemotherapy-induced nausea and vomiting on daily life (63.5% v 55.6%; P = .019). Both treatments were well tolerated. While there was an absolute difference of 8.3% in the overall CR favoring the palonosetron group, the most pronounced effect of aprepitant was seen in the prevention of vomiting with an absolute difference of 17% between the aprepitant regimen and the control regimen. The authors concluded that the aprepitant regimen was more effective than the control regimen for prevention of chemotherapy-induced nausea and vomiting in patients receiving both an anthracycline and cyclophosphamide.

Extending the study by Warr et al, Herrstedt et al studied the efficacy and tolerability of ondansetron plus dexamethasone ± aprepitant over multiple chemotherapy cycles in a prospective, multicenter, randomized, double-blind study in 744 breast cancer patients naïve to emetogenic chemotherapy who were treated with up to four cycles of cyclophosphamide ± doxorubicin or epirubicin.[5] The study medication schedule is shown in Table 1 in Appendix A. Treatment groups were similar with respect to baseline characteristics including race, age, sex, history of motion sickness, and history of vomiting during pregnancy. The percentage of patients who experienced an overall CR (defined as no vomiting and no use of rescue therapy during the 120 hours after the initiation of the first chemotherapy cycle) in cycle 1 and who sustained an overall complete response over cycles 2 – 4 was greater with the aprepitant regimen than with the control regimen (P = 0.017). Emesis was significantly better controlled in the aprepitant group whereas nausea, although favoring the aprepitant regimen, was not significantly different between treatment arms. The most pronounced effect of aprepitant, the prevention of vomiting with an absolute difference of 17% between the aprepitant regimen and the control regimen in cycle one, was not only maintained over four cycles but increased to a 24% absolute difference in cycle 4. Both treatments were well tolerated. The authors concluded the aprepitant regimen was more effective than the control regimen for the prevention of nausea and emesis induced by MEC over multiple chemotherapy cycles.

Rapoport et al demonstrated the efficacy of aprepitant in patients receiving a broad range of MEC.[6] In a prospective, multicenter, randomized, double-blind, phase III study in 848 patients naïve to MEC or HEC, Rapoport et al compared the efficacy and tolerability of ondansetron plus dexamethasone ± aprepitant after one cycle in patients receiving MEC including oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin,

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[4] Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy J Clin Oncol 2005; 23: 2822-2830.

[5] Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer 2005; 104:1548-1555.

[6] Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer 2010;18: 423-431.

cyclophosphamide (< 1,500 mg/m^2), and cytarabine (> 1 gm/m^2). The study medication schedule is shown in Table 1 in Appendix A. The control regimen (ondansetron + dexamethasone) was given to 418 patients and the aprepitant regimen (ondansetron+ dexamethasone+ aprepitant) to 430 patients. Treatment arms were similar with respect to baseline patient characteristics including sex, age, history of motion sickness, and history of vomiting during pregnancy. Breast cancer was the most common diagnosed malignancy (52% of randomized patients), followed by colorectal cancer (20%), lung cancer (13%), and ovarian cancer (4.6%). The overall CR (defined as no vomiting and no use of rescue therapy during the 120 hours after the initiation of the first chemotherapy cycle) for all chemotherapy agents was significantly higher for the aprepitant regimen than for the control regimen (68.7% vs 56.3%, $p < 0.001$). When considering only patients who received doxorubicin plus cyclophosphamide (AC) based chemotherapies, confirming the results reported in the Warr and Herrstedt studies, the overall CR rate was higher for the aprepitant regimen than the control regimen (62.8% vs 47.1%, $p < 0.05$). When excluding patients who received doxorubicin plus cyclophosphamide based chemotherapy, the CR rate was higher for the aprepitant regimen than the control regimen (73.9% aprepitant regimen; 65.5% control regimen). Both treatments were well tolerated. No significant differences between aprepitant and control regimens were identified in adverse event categories. In summary, during the 120 hour period post chemotherapy, patients receiving MEC and aprepitant had an absolute difference in CR over the control group of 12.4%. The authors concluded that the aprepitant regimen provided superior efficacy in the treatment of chemotherapy-induced nausea and vomiting in a broad range of patients receiving MEC (non-AC or AC based) in both no vomiting and CR endpoints.

Jin et al performed a meta-analysis of 15 trials involving 4,798 patients who received MEC or HEC to assess the safety and antiemetic efficacy of aprepitant. Studies included for analysis were those that were randomized controlled, compared the antiemetic efficacy of aprepitant with a placebo or no intervention for the prophylaxis of chemotherapy-induced nausea and vomiting, and contained information regarding the complete control of vomiting and/or nausea during the first 24 hours and/or after the first 24 hours after chemotherapy administration. Compared with placebo or the standard antiemetic therapy, the cumulative incidence of emesis was significantly reduced in patients treated with aprepitant-based therapy on the first day [relative risk (RR) = 1.13, 95% confidence interval (CI) 1.10 – 1.16, from 2 to 5 days (RR = 1.35, 95% CI 1.22 – 1.48), and in the overall 5 days (RR = 1.30, 95% CI 1.22 – 1.39). There was no significant difference in safety between aprepitant-based and non-aprepitant-based regimens. The authors concluded that aprepitant with 5-HT3 receptor antagonists and dexamethasone is highly effective in preventing nausea and vomiting in the days after administration of MEC or HEC.

2. Published Evidence-Based Guidelines

Several evidenced based guidelines endorse the use of aprepitant along with 5-HT3 antagonists and dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in patients receiving MEC. Of note, these guidelines also allow for the interchangeable use of oral, transdermal and intravenous formulations for each of the antiemetics. As mentioned earlier, as the ASHP guidelines have not been updated since 1999, they are not included in this document. The National Comprehensive Cancer Network (NCCN)[7] publishes clinical practice guidelines for antiemesis that consist of the authors' consensus of generally accepted treatment protocols. The 2012 guidelines recommend consideration of aprepitant use per the FDA-labeled indications for both HEC and MEC regimens. Furthermore, in addition to an all oral antiemetic combination of a 5-HT3 antagonist, dexamethasone, and aprepitant, the guidelines allow for the use of transdermal or intravenous 5-HT3 antagonists including palonosetron, intravenous dexamethasone, and intravenous aprepitant in their recommended antiemetic combination regimens for both HEC and MEC treatments.

[7] Antiemesis. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). Version 1.2012.

The American Society of Clinical Oncology (ASCO)[8] publishes antiemetic clinical practice guidelines based upon a systematic review and analysis of the medical literature. The 2011 guidelines recommend consideration of aprepitant use per the FDA-labeled indications for both HEC and MEC regimens. As with the NCCN guidelines, ASCO allows for the use of transdermal or intravenous 5-HT3 antagonists including palonosetron, intravenous dexamethasone, and intravenous aprepitant in their recommended antiemetic combination regimens for both HEC and MEC treatments.

The Multinational Association for Supportive Care in Cancer (MASCC)[9] publishes clinical practice guidelines for the prevention of chemotherapy nausea and vomiting based upon a review and analysis of published evidence. The 2010 guidelines recommend consideration of aprepitant use per the FDA-labeled indications for both HEC and MEC regimens. As with NCCN and ASCO, MASCC allows for the interchangeable use of oral or intravenous formulations of antiemetics within the guidelines.

In summary, each organization concurs that the combination of a 5-HT3 antagonist (dolasetron, granisetron, ondansetron, palonosetron), dexamethasone, and aprepitant, either using oral, transdermal, or intravenous formulations, is reasonable and necessary in patients receiving either HEC or MEC.

3. Authoritative Drug Compendia

Summaries for aprepitant taken from the drug compendia recognized by The Centers for Medicare & Medicaid Services under the following authorities:

- §1861(t)(2)(B), which allows the Secretary to revise the list of compendia in clause (ii)(I); and
- §1873, which allows the Secretary to recognize a successor publication if one of the statutorily designated publication changes its name

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- Aprepitant and fosaprepitant dimeglumine are used in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC to HEC, including high-dose cisplatin therapy in adults.

Elsevier Gold Standard's Clinical Pharmacology

- Aprepitant is used for chemotherapy-induced nausea/vomiting (CINV) prophylaxis associated with moderately-emetogenic chemotherapy
- Aprepitant is used for chemotherapy-induced nausea/vomiting (CINV) prophylaxis associated with highly-emetogenic chemotherapy

The National Comprehensive Cancer Network (NCCN) Drugs and Biologic Compendium™

- Aprepitant use in combination with dexamethasone and a serotonin antagonist with or without lorazepam, histamine-2 blockers, or proton pump inhibitors
    - before high emetic risk chemotherapy
    - before moderate emetic risk chemotherapy for select patients
- Aprepitant use with or without lorazepam, histamine-2 blockers, or proton pump inhibitors
    - after high emetic risk chemotherapy in combination with dexamethasone
    - after moderate emetic risk chemotherapy for select patients with or without dexamethasone

[8] Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Practice Guideline Update. J Clinical Oncology 2011; 29:4184-4198.

[9] Roila F, Herrstedt J, Aapro M et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Anns Oncol 2010; 21 (Supplement 5): v232-243.

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- Aprepitant is indicated, in combination with other antiemetics, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin
- Aprepitant is indicated, in combination with other antiemetics, for the prevention of nausea and vomiting associated with initial and repeat courses of MEC

In summary, evidence from three well designed clinical trials demonstrate the 3-drug antiemetic combination of aprepitant, dexamethasone, and ondansetron improves the complete response rate defined as no emesis and no rescue mediation in the 120 hour period following chemotherapy by an absolute increase in CR rate of 8.3 – 24% in patients receiving MEC. The use of this 3-drug antiemetic regimen for prevention of nausea and vomiting associated with MEC is endorsed by published evidenced based guidelines and authoritative drug compendia.

Recommendation for Future Inclusion of HEC and MEC Agents

To avoid the need for an NCD reconsideration for each new HEC or MEC agent that becomes FDA approved in the future, include wording in the NCD to allow coverage for the 3-drug antiemetic combination of aprepitant, dexamethasone, and 5-HT3 antagonists for those new medications that, consistent with the aprepitant Decision Memo, would be classified as either HEC or MEC using the Hesketh method or in at least two published evidence-based guidelines.

New Evidence to Support the Inclusion of Palonosetron and Allow the Use of Therapeutically Equivalent Doses of Any Available 5-HT3 Antagonist, Dexamethasone, and Aprepitant Formulations (Oral, Transdermal, Intravenous*)*

The current NCD specifies coverage for aprepitant when used with dexamethasone and one of the oral formulations of the 5-HT3 antagonists dolasetron, granisetron, or ondansetron. Palonosetron, a second generation 5-HT3 antagonist, is FDA approved for:

- MEC – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- HEC – prevention of acute nausea and vomiting associated with initial and repeat courses.[10]

A discussion of the clinical support of palonosetron in comparison to first generation 5-HT3 antagonists for MEC and HEC will follow. Additionally, palonosetron combined with aprepitant and dexamethasone has been shown to be a safe and effective antiemetic combination for both MEC and HEC.

Transdermal and injectable formulations of 5-HT3 antagonists are considered in evidenced based guidelines (NCCN, ASCO) to have the same therapeutic effect as oral formulations if used in equivalent doses. It would be beneficial to have all 5-HT3 antagonists and their various formulations available for use in cancer patients. There may be situations where the use of an agent or formulation outside the current restricted NCD list is preferable and should be considered for coverage. Examples of such situations include:

- Patients intolerant (headache) to one 5-HT3 antagonist, may tolerate a different 5-HT3 antagonist in subsequent therapies.[11]
- Patients unresponsive (developed nausea and vomiting) to one 5-HT3 antagonist may respond to another 5-HT3 antagonist in subsequent therapies. Palonosetron, shown to have superior efficacy to ondansetron in patients receiving both HEC and MEC, is often given to patients who were unresponsive to ondansetron in an earlier treatment.[12, 13, 14]

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[10] Aloxi (palonosetron package insert. Eisai Inc. 6/2009.

[11] Personal Communication. Michael J. Berger, PharmD, BCOP, Specialty Practice Pharmacist, Department of Pharmacy, The James Cancer Hospital at The Ohio State University, The Stefanie Spielman Comprehensive Breast Center, 1145 Olentangy River Rd, Room 4038 Columbus, OH 43212. Ph: 614-293-0191, e-mail: michael.berger@osumc.edu.

[12] Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Anns Oncol 2006; 17:1441-1449.

- Patients initiated on palonosetron-based antiemetic therapy not containing aprepitant consistent with nationally recognized guidelines occasionally are unresponsive to treatment necessitating the addition of an antiemetic (aprepitant) with a different mechanism of action in subsequent administration of the same chemotherapy regimen.[15]
    - If the combination of palonosetron, dexamethasone, and aprepitant were effective, the antiemetic combination is usually continued rather than switching back to an ondansetron-based antiemetic regimen if the need arises to change the patient to another chemotherapy regimen of similar emetogenic potential.
- For clarification purposes, the proposed addition of an antiemetic in patients who were unresponsive to an earlier antiemetic regimen, the addition of aprepitant would occur in subsequent chemotherapy treatments as opposed to use while the patient is vomiting.

1. Clinical Research and Evidence

Gralla, Eisenberg, Aapro, and Saito performed research demonstrating palonosetron was superior to first-generation 5-HT3 antagonists in patients receiving MEC or HEC. Their research findings are summarized below.

Gralla et al performed a prospective, multicenter, randomized, double-blind, phase III study in 563 evaluable patients who were either chemotherapy naïve or non-naïve (having experienced a maximum of mild nausea previously) and scheduled to receive any dose from the following MEC agents: carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, or mitoxantrone; methotrexate ≥ 250 mg/m^2, cyclophosphamide < 1,500 mg/m^2, doxorubicin > 25 mg/m^2, or cisplatin < 50 mg/m^2.[16] Patients received either single doses of intravenous palonosetron 0.25 mg, palonosetron 0.75 mg or ondansetron 32 mg 30 minutes prior to chemotherapy. Patients did not receive dexamethasone. The three treatment arms were similar in terms of patient age, gender, ethnicity, tobacco use, alcohol use, and prior chemotherapy history. Table 2 in Appendix A shows CR (defined as no emetic episodes and no rescue medication) rates were significantly higher for palonosetron 0.25 mg than ondansetron during the acute and overall periods post chemotherapy. CR rates achieved with palonosetron 0.75 mg were numerically higher but not statistically significant from ondansetron during all time intervals. Both treatments were well tolerated. In summary, there was an absolute difference of 19% in the overall CR favoring the palonosetron 0.25 mg group. The authors concluded that palonosetron was superior to ondansetron in this setting.

Eisenberg et al performed prospective, multicenter randomized, double-blind, phase III study in 569 evaluable patients who were either chemotherapy naïve or non-naïve (having experienced a maximum of mild nausea previously) and scheduled to receive any dose from the following MEC agents: carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, or mitoxantrone; methotrexate ≥ 250 mg/m^2, cyclophosphamide < 1,500 mg/m^2, doxorubicin > 25 mg/m^2, or cisplatin < 50

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[13] Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Anns Oncol 2003; 14:1570-1577.

[14] Massa E, Astara G, Madeddu C, et al. Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pre-treated patients who failed to respond to previous antiemetic treatment: comparison between elderly and non-elderly patient response. Crit Rev Oncology/Hematology 2009; 70:83-91

[15] Oechsle K, Muller MR, Hartmann JT, et al. Aprepitant as salvage therapy in patients with chemotherapy-induced nausea and emesis refractory to prophylaxis with 5-HT3 antagonists and dexamethasone. Onkologie 2006; 29:557-561.

[16] Gralla R, Lichinitser M, Van der Vegt, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Anns Oncol 2003; 14:1570-1577.

mg/m^2.[17] Patients received either single doses of intravenous palonosetron 0.25 mg, palonosetron 0.75 mg or dolasetron 100 mg 30 minutes prior to chemotherapy. Use of corticosteroids was at the physician discretion. The three treatment arms were similar in terms of patient age, gender, ethnicity, tobacco use, alcohol use, prior chemotherapy history, and corticosteroid use. Table 3 in Appendix A shows CR (defined as no emetic episodes and no rescue medication) rates during the first 24 hours post chemotherapy were numerically higher for palonosetron 0.25 mg and in the palonosetron 0.75 mg group compared with the dolasetron group. CR rates were significantly higher for the palonosetron 0.25 mg and palonosetron 0.75 mg groups compared with dolasetron during the delayed period and for palonosetron 0.25 mg and palonosetron 0.75 mg versus dolasetron during the overall period. Both treatments were well tolerated. In summary, there was an absolute difference of 12% in the overall CR favoring the palonosetron 0.25 mg group. The authors concluded that a single palonosetron dose is as effective as a singe dolasetron dose in preventing acute nausea and vomiting and superior to dolasetron in preventing delayed nausea and vomiting after MEC.

Aapro et al performed a prospective, multicenter, randomized, double-blind, double-dummy phase III study in 667 evaluable patients who were naïve or non-naïve to chemotherapy and scheduled to receive any of the following HEC agents: cisplatin ≥ 60 mg/m^2, cyclophosphamide > 1,500 mg/m^2, carmustine > 250 mg/m^2, dacarbazine, or mechlorethamine.[18] Patients received either single doses of intravenous palonosetron 0.25 mg, palonosetron 0.75 mg or ondansetron 32 mg 30 minutes prior to chemotherapy. A single dose of dexamethasone prior to chemotherapy was at the physician discretion. The three treatment arms were similar in terms of patient age, gender, ethnicity, alcohol use, prior chemotherapy history, underlying diagnosis, administered chemotherapy agents, and dexamethasone use. Table 4 in Appendix A shows palonosetron arms were at least as effective as ondansetron in preventing nausea and vomiting during the 0-24 hour period post chemotherapy. CR (defined as no emetic episodes and no rescue medication) rates were slightly higher with palonosetron than ondansetron during the delayed and overall phases. For the subgroup of patients also receiving dexamethasone, CR rates for patients treated with palonosetron 0.25 mg or 0.75 mg and dexamethasone day 1 were numerically higher than for those patients treated with ondansetron plus dexamethasone during the 0-24 time period following chemotherapy. For the delayed (24-120 hours post chemotherapy) and overall phases (0-120 hours post chemotherapy), significantly higher CR rates were seen for single doses of palonosetron 0.25 mg plus dexamethasone compared with ondansetron plus dexamethasone (42% versus 28.6%; P = 0.021 and 40.7% versus 25.2%; P = 0.005, respectively). Both palonosetron and ondansetron were well tolerated. In summary, there was an absolute difference of 15.5% in the overall CR favoring the palonosetron 0.25 mg group. The authors concluded that single dose palonosetron was as effective as ondansetron in preventing acute nausea and vomiting following HEC, and with dexamethasone pre-treatment, its effectiveness was significantly increased over ondansetron throughout the 120 hour period following chemotherapy.

Saito et al performed a prospective, multicenter, randomized, double-blind, double-dummy phase III study in 1114 patients evaluable for efficacy who were naive or non-naïve (had been treated with one low or minimally emetogenic chemotherapy drug per NCCN classification) and scheduled to receive HEC including cisplatin ≥ 50 mg/m^2, doxorubicin or epirubicin plus cyclophosphamide.[19] Patients received dexamethasone plus either palonosetron 0.75 mg or granisetron 40 mcg/kg 30 minutes prior to chemotherapy. Treatment arms were similar in terms of patient age, sex, tumor type, previous chemotherapy, previous surgery, previous radiotherapy, and alcohol consumption. CR (defined as no emetic

[17] Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist. Cancer 2003; 98:2473-2482.

[18] Aapro MS, Grunberg SM, Manikhas GM, et al. a phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Anns Oncol 2006; 17:1441-1449.

[19] Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomized, comparative phase III trial. Lancet Oncol 2009; 10:115-124.

episodes and no rescue medication) rates for patients treated with palonosetron and granisetron were similar in both arms during the 0-24 hours following chemotherapy (75.3% versus 73.3%, respectively; mean difference 2.9% [95% CI -2.70 to 7.27]). The CR rate during the 24-120 hour period following chemotherapy was significant higher in the palonosetron group than in the granisetron group (56.8 % versus 4.5%, respectively; P < 0.0001). Both treatment arms had comparable safety profiles. In summary, in this setting, there was an absolute difference of 11.1% in the overall (0-120 hour period post chemotherapy) CR favoring the palonosetron 0.25 mg group. The authors concluded that when administered with dexamethasone before highly emetogenic chemotherapy, palonosetron exerts efficacy against chemotherapy-induced nausea and vomiting which is non-inferior to that of granisetron during the 0-24 hour period post chemotherapy and better than that of granisetron in the period of 24-120 hours following chemotherapy.

Botrel et al performed a meta-analysis of 5 studies to compare the efficacy of palonosetron to other 5-HT3 antagonists in preventing chemotherapy-induced nausea and vomiting in patients receiving MEC or HEC.[20] The authors concluded palonosetron was more effective than the other 5-HT3 antagonists in preventing acute and delayed chemotherapy-induced nausea and vomiting in patients receiving MEC or HEC treatments, regardless of the use of concomitant corticosteroids.

Grote et al performed a prospective, multicenter phase II open-label study to evaluate the safety and efficacy of the 3 drug combination of aprepitant, palonosetron, and dexamethasone in 58 evaluable patients scheduled to receive at least one of the following MEC agents: carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, mitoxantrone, or oxaliplatin; methotrexate > 250 mg/m^2, cyclophosphamide < 1,500 mg/m^2, doxorubicin > 25 mg/m^2, or cisplatin ≤ 50 mg/m^2.[21] Patients received oral aprepitant 125 mg, oral dexamethasone 12 mg, and intravenous palonosetron 0.25 mg on day 1 followed by oral aprepitant 80 mg and oral dexamethasone 8 mg on days 2 and 3 after chemotherapy. The median patient age was 60 years, 78% of patients were female, 71% were white, 47% were being treated for breast cancer, and 45% were chemotherapy naïve. The CR (defined as no emetic episodes and no rescue medication) rates were 88% during the 0-24 hour period post chemotherapy, 78% during the 24-120 hour period post chemotherapy, and 78% over the 0-120 hour period following chemotherapy. Treatment was well tolerated. The authors concluded that palonosetron in combination with dexamethasone and aprepitant is safe and highly effective in preventing chemotherapy-induced nausea and vomiting in the days following administration of MEC.

Longo et al performed a prospective, phase II study in 222 chemotherapy naïve patients to evaluate the safety and efficacy of the 3 drug combination of aprepitant, palonosetron, and dexamethasone in patients receiving HEC cisplatin-based (≥ 50 mg/m^2) anticancer chemotherapy.[22] Patients received oral aprepitant 125 mg, intravenous dexamethasone 20 mg and intravenous palonosetron 0.25 mg on day 1 followed by oral aprepitant 80 mg and oral dexamethasone 4 mg on days 2 and 3 after chemotherapy. The median patient age was 62 years, 76.6% of patients were male, and the most common tumors were lung (66.7%) and head and neck (15.8%). The overall CR (defined as no emetic episodes and no rescue medication during the 0-120 hour period following chemotherapy) rate was 70.3%. Treatment was well tolerated. The authors concluded that palonosetron in combination with dexamethasone and aprepitant is effective to prevent chemotherapy-included nausea and vomiting in patients treated with cisplatin-based HEC.

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[20] Botrel TEA, Clark OAC, C L, et al. Efficacy of palonosetron compared to other serotonin inhibitors in preventing chemotherapy-induced nausea and vomiting in patients receiving moderately or highly emetogenic treatment: systematic review and meta-analysis. Supp Care Cancer 2011; 19:823-832.

[21] Grote T, Hajdenberg J, Cartmell A, et al. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. J Support Oncol 2006; 4:403-408.

[22] Longo F, Mansueto G, Lapadula V, et al. Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2011; 19:1159-1164.

2. Published Evidence-Based Guidelines

NCCN, ASCO, MASCC evidence-based guidelines reflect the clinical data. The 3-drug antiemetic combination consisting of a 5-HT3 antagonist (any among dolasetron, granisetron, ondansetron, or palonosetron), dexamethasone, and aprepitant is recommended for patients receiving both MEC and HEC. Palonosetron is the preferred 5-HT3 antagonist recommended by NCCN for both MEC and HEC. The guidelines also allow for the use of therapeutic equivalent doses of medications given by intravenous, oral, or transdermal routes of administration. NCCN states oral and intravenous 5-HT3 antagonists have equal efficacy when used at the appropriate doses.

3. Authoritative Drug Compendia

Summaries for palonosetron taken from the drug compendia recognized by The Centers for Medicare & Medicaid Services under the following authorities:

- §1861(t)(2)(B), which allows the Secretary to revise the list of compendia in clause (ii)(I); and
- §1873, which allows the Secretary to recognize a successor publication if one of the statutorily designated publication changes its name

American Hospital Formulary Service-Drug Information (AFHS-DI)®

- Palonosetron hydrochloride is used IV for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Palonosetron is also used IV for the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

Elsevier Gold Standard's Clinical Pharmacology

- Palonosetron is used for acute chemotherapy-induced nausea/vomiting (CINV) prophylaxis associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Palonosetron is used for acute chemotherapy-induced nausea/vomiting (CINV) prophylaxis associated with initial and repeat courses of highly emetogenic cancer chemotherapy

The National Comprehensive Cancer Network (NCCN) Drugs and Biologic Compendium™

- Preferred agent in combination with dexamethasone with or without lorazepam, histamine-2 blockers, or proton pump inhibitors
    - Before high emetic risk chemotherapy in combination with aprepitant or fosaprepitant
    - Before moderate emetic risk chemotherapy with or without aprepitant or fosaprepitant

Thomson Micromedex DrugDex®

- Palonosetron injection is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of MEC and HEC

In summary, evidence from well-designed clinical trials demonstrate that the antiemetic regimen of dexamethasone and palonosetron improves the overall CR (defined as no emesis and no rescue medication in the 120 hour period following MEC) by an absolute 12-19% when compared with dexamethasone combined with either ondansetron or granisetron. In patients receiving HEC, palonosetron was shown to improve the overall CR (defined as no emesis and no rescue medication in the 120 hour period following HEC) by an absolute 11.1 – 15.5% when compared with dexamethasone combined with either ondansetron or granisetron. The 3-drug antiemetic combination of aprepitant, palonosetron, and dexamethasone was shown to be safe and effective in preventing nausea and vomiting associated with MEC or HEC. The use of dexamethasone and palonosetron in preventing nausea and vomiting associated with MEC or HEC is endorsed by published evidenced-based guidelines and authoritative drug compendia.

Additional Recommendations

Recommendation: Allow for oral dexamethasone taken by the patient at home during the time period of chemotherapy administration.

Most anticancer chemotherapy agents are administered in combinations (regimens) that achieve better response rates than individual agents used alone. Combinations may require considerations that cut across all components of the regimen. For example, the cisplatin plus pemetrexed regimen used for the treatment of non-small cell lung cancer uses oral dexamethasone for two reasons. First, oral dexamethasone is used the day before, day of, and day after pemetrexed administration to minimize the incidence and severity of skin reactions secondary to pemetrexed as recommended within the package insert.[23] And second, dexamethasone is used as part of the antiemetic combination for the chemotherapy. Patients typically are given a three day prescription for oral dexamethasone to be dispensed from their local pharmacy so they can begin premedication the day prior to pemetrexed and continue through the treatment. This standard of care practice simplifies patient medication ordering and minimizes patient confusion when compared to the practice of dividing the order up into a prescription for dexamethasone use at home prior to and following pemetrexed but administering a dose in clinic the day of treatment. Similarly, oral dexamethasone prescriptions are given to patients for use with docetaxel or paclitaxel based anticancer chemotherapy regimens to minimize the incidence and severity of fluid retention and/or hypersensitivity reactions associated with these chemotherapy agents.[24, 25]

Recommendation: Allow for the intravenous administration of dexamethasone in place of oral dexamethasone.

It is standard of care for physicians to choose to use intravenous dexamethasone in place of oral dexamethasone premedication in various situations. For patients determined the day of treatment to be non-compliant in taking their oral dexamethasone prescribed to be taken at home, physicians may decide to administer intravenous dexamethasone the day of chemotherapy administration. Although as mentioned earlier, oral dexamethasone prescriptions are given to patients for use with docetaxel or paclitaxel based anticancer chemotherapy regimens, it is often more convenient and considered therapeutically equivalent to administer the dexamethasone intravenously the day of chemotherapy administration.[26, 27, 28]

On occasion, patients may experience a hypersensitivity reaction to an anticancer chemotherapy agent even though they are receiving oral dexamethasone as a component of an antiemetic regimen. Physicians may choose to continue subsequent therapies with the same offending agent but employ intravenous dexamethasone and a slower infusion rate in an attempt to reduce the incidence and severity of additional hypersensitivity reactions.

In summary, there are several standards of care situations where patients receive oral dexamethasone by taking the medication at home or receive the dexamethasone intravenously in clinic. Either way, patients are receiving the same pharmacologic agent that functions as an antiemetic. Situations such as described should be covered in the Aprepitant NCD.

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[23] Alimta (pemetrexed) package insert. Eli Lilly and Company. Indianapolis, IN, 46285. 11/2011.

[24] Taxotere (docetaxel) package insert. Sanofi-Aventis. Bridgewater, NJ, 08807. 5/2010.

[25] Taxol (paclitaxel) package insert. Bristol-Myers Squibb Company. Princeton, NJ, 08543. 4/2011.

[26] Markman M, Kennedy A, Webster K, et al. An effective and more convenient drug regimen for prophylaxis against paclitaxel-associated hypersensitivity reactions. J Cancer Res Clin Oncol 1999; 125:427-429.

[27] Chouhan JD, Herrington JD. Single premedication dose of dexamethasone 20 mg IV before docetaxel administration. J Oncol Pharm Practice. 2010; 17:155-159.

[28] Rosenberg P, Andersson H, Boman K, et al. Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. Acta Oncologica 2002; 41:418-424.

Recommendation: Allow for aprepitant in combination with 5-HT3 antagonists in patients shown to be dexamethasone (corticosteroid) intolerant or if the physician wishes to avoid dexamethasone (corticosteroid) because the patient is a diabetic.
There are situations where physicians may not wish to administer dexamethasone to a patient as part of an antiemetic regimen. Patients may have been determined to be dexamethasone intolerant in an earlier course of therapy. To avoid the adverse drug reaction, physicians may opt to administer a 5-HT3 antagonist plus aprepitant but without dexamethasone in subsequent therapies.

Alternately, patients may be diabetics whose blood sugar control may be jeopardized by dexamethasone administration. Physicians may opt to use a 5-HT3 antagonist plus aprepitant but without dexamethasone in such patients to avoid loss of diabetic control.

Reconsideration Request Conclusion
Since the Aprepitant NCD became effective in 2005, new information relevant to the use of this medication has become available. The manufacturer received expanded FDA approval for aprepitant use in the prevention of nausea and vomiting associated with MEC based on clinical trials demonstrating an improvement in absolute CRs of 8.3 – 24%. The combination of dexamethasone and palonosetron has been shown to be superior to dexamethasone plus dolasetron, granisetron or ondansetron in preventing nausea and vomiting associated with MEC or HEC. Emetogenic classifications have been updated to include new anticancer chemotherapy agents. Published evidence based guidelines have been updated to include new anticancer chemotherapy drugs and the incorporation of research data into antiemetic recommendations. Methods to administer chemotherapy have evolved to fit the outpatient setting. For the benefit of patients, an update of the Aprepitant NCD should be undertaken taking into account the information provided.

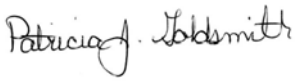
Proposed Aprepitant NCD Reconsideration Wording
To incorporate the information presented within this reconsideration, please consider changing the current NCD to read: The evidence is adequate to conclude that the use of the antiemetic 3-drug combination of aprepitant, a 5-HT3 antagonist (dolasetron, granisetron, ondansetron, palonosetron) and dexamethasone using therapeutically equivalent doses of any available pharmaceutical formulation (intravenous, oral, transdermal) is reasonable and necessary for a specific patient population. We define the patient population for which the use of the 3-drug antiemetic combination is reasonable and necessary as only those patients who are receiving one or more current or future anticancer chemotherapy agents classified as moderately or highly emetogenic using the Hesketh classification system or classified as moderately or highly emetogenic in at least two published evidence based guidelines. Using Hesketh and evidence based guidelines, current anticancer chemotherapy agents classified as moderately or highly emetogenic include: carmustine, cisplatin, cyclophosphamide, dacarbazine, mechlorethamine, streptozocin, doxorubicin, epirubicin, lomustine, alemtuzumab, azacitidine, bendamustine, carboplatin, clofarabine, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Patients documented to have taken oral dexamethasone at home are an acceptable alternative to on-site clinic administration of the medication.

In patients documented to be intolerant of or in whom use of dexamethasone may be relatively contraindicated (diabetic), dexamethasone may be omitted from the 3-drug antiemetic regimen at the physician discretion.

NCCN appreciates the opportunity to share this new evidence with CMS. We believe that our reconsideration request will provide useful data for CMS to consider as its staff work to consider the development of a revised NCD for Aprepitant for Chemotherapy-Induced Emesis. If you would like any further information, please contact me personally by phone at (215) 690-0269 or by email at goldsmith@nccn.org. Alternatively, you may contact Jessica DeMartino, PhD Manager of Health Policy Programs at (215) 690-0245 or by email demartino@nccn.org. Thank you for your attention to these important matters.

Regards,



Patricia J. Goldsmith
Executive Vice President & Chief Operating Officer

Cc: Lori Ashby, James Rollins, MD

Appendices:
A – Tables
B – Supporting Documents and References (Attached as separate document)

Appendix A: Supporting Tables

Table 1

Warr et al, Herrstedt et al, and Rapoport et al Study Medication Schedule			
Dose			
Regimen and Study Medication	**Day 1**	**Day 2**	**Day 3**
Aprepitant Regimen			
Aprepitant	**125 mg orally 1 hour before chemotherapy**	**80 mg orally**	**80 mg orally**
Ondansetron	**8 mg orally 30 – 60 minutes before and 8 hours after first chemotherapy dose**	**Placebo twice each day**	**Placebo twice each day**
Dexamethasone	**12 mg orally 30 minutes before chemotherapy**		
Control Regimen			
Aprepitant	**Oral placebo**	**Oral placebo**	**Oral placebo**
Ondansetron	**8 mg orally 30 – 60 minutes before and 8 hours after first chemotherapy dose**	**8 mg orally twice each day**	**8 mg orally twice each day**
Dexamethasone	**20 mg orally 30 minutes before chemotherapy**		

Table 2

Gralla et al Complete Response rates (ITT cohort, n = 563)							
Time Period (Hours)	**PAL 0.25 mg (n = 189)**			**PAL 0.75 mg (n = 189)**			**OND 32 mg (n = 185)**
	%	**PAL minus OND 97.5% CI[a]**	**P value[b]**	**%**	**PAL minus OND 97.5% CI[a]**	**P value[b]**	**%**
Acute (0-24)	**81**	**1.8% to 22.8%**	**0.0085**	**73.5**	**-6.1% to 15.9%**	**0.3067**	**68.6**
Delayed (24-120)	**74.1**	**7.5% to 30.3%**	**< 0.001**	**64.6**	**-2.4% to 21.3%**	**0.0730**	**55.1**
Overall (0-120)	**69.3**	**7.4% to 30.7%**	**< 0.001**	**58.7**	**-3.6% to 20.5%**	**0.1192**	**50.3**

[a]97.5%CIs for the difference between PAL 0.25 mg or 0.75 mg dose group and the OND group indicate PAL superiority

[b]P values represent adjusted post hoc, two-sided, Fisher's exact test comparisons of PAL with OND. Comparisons are significant at the 0.025 level.

CI, confidence interval; ITT, intention-to treat; PAL = Palonosetron; OND = Ondansetron

Table 3

Eisenberg et al Complete Response rates (ITT cohort, n = 569)							
Time Period (Hours)	**PAL 0.25 mg (n = 189)**			**PAL 0.75 mg (n = 189)**			**DOL 100 mg (n = 191)**
	%	**PAL minus DOL 97.5% CI**	**P value**	**%**	**PAL minus DOL 97.5% CI**	**P value**	**%**
Acute (0-24)	**63**	**-1.7% to 21.9%**	**0.049**	**57.1**	**-7.7% to 16.2%**	**0.412**	**52.9**
Delayed (24-120)	**54**	**3.4% to 27.1%[a]**	**0.004[b]**	**56.6**	**6% to 29.7%[a]**	**< 0.001[b]**	**38.7**
Overall (0-120)	**46**	**0.3% to 23.7%[a]**	**0.021[b]**	**47.1**	**1.3% to 24.8%[a]**	**0.012[b]**	**34**

[a]97.5%CIs for the difference between PAL 0.25 mg or 0.75 mg dose group and the DOL group indicate PAL superiority

[b]P values represent adjusted, post hoc, two-sided, Fisher's exact test comparisons of PAL with DOL. Comparisons are significant at the 0.025 level.

CI, confidence interval; ITT, intention-to treat; PAL = Palonosetron; DOL = Dolasetron

Table 4

Aapro et al Complete Response rates (ITT cohort, n = 667)							
Time Period (Hours)	**PAL 0.25 mg (n = 223)**			**PAL 0.75 mg (n = 223)**			**OND 32 mg (n = 221)**
	%	**PAL minus OND 97.5% CI**	**P value[a]**	**%**	**PAL minus OND 97.5% CI**	**P value[a]**	**%**
Acute (0-24)	**59.2**	**-8.8% to 13.1%**	**0.701**	**65.5**	**-2.3% to 19.2%**	**0.079**	**57**
Delayed (24-120)	**45.3**	**-4.6% to 17.3%**	**0..180**	**48**	**-1.9% to 20%**	**0.056**	**38.9**
Overall (0-120)	**40.8**	**-2.9% to 18.5%**	**0.095**	**42.2**	**-1.6% to 19.8%**	**0.051**	**33**

[a]P values represent adjusted, post hoc, two-sided, Fisher's exact test comparisons of PAL with DOL. Comparisons are significant at the 0.025 level.

CI, confidence interval; ITT, intention-to treat; PAL = Palonosetron; OND = Ondansetron