

Project Name: Antiemetics  
 Project ID: CANM0509

Table 2: Public Review Comments

Reviewer Name <sup>1</sup>	Reviewer Affiliation <sup>2</sup>	Section <sup>3</sup>	Reviewer Comments	Author Response <sup>4</sup>
Mike Neuss	American Society of Clinical Oncology	General	ASCO is a 27,000 member national organization, representing physicians and other healthcare professionals involved in cancer treatment, diagnosis, prevention and research. ASCO members also conduct research leading to improved patient outcomes. We are committed to ensuring that evidence-based practices for the prevention, diagnosis and treatment of cancer are available to all patients, and we appreciate the opportunity to comment on this draft Technology Assessment (TA).	Thank you.
Mike Neuss	American Society of Clinical Oncology	General	The 2006 ASCO guideline on the use of antiemetics for CINV [Kris, JCO, 2006] considered a number of additional studies for its recommendation that patients undergoing highly emetogenic chemotherapy receive three days of aprepitant [Chawla, Cancer, 2003; Hesketh, JCO, 2003; Poli-Bigelli, Cancer, 2003]. Additional studies that should be considered when examining dosing regimens for aprepitant include the pivotal trial completed to obtain FDA approval for aprepitant, which was also the basis for the currently approved dosing. We recognize that these studies may not meet the inclusion criteria specified for this review, but they are in fact important to consider if dosing regimens for aprepitant are being evaluated.	Hesketh 2003 and Poli-Bigelli are the pivotal trials and are included. Added clarification in report.
Mike Neuss	American Society of Clinical Oncology	General	Finally, although this was clearly beyond the scope of your review, a critical patient care issue should also not be overlooked: it could be argued that the real issue is access to aprepitant and the hidden costs of breakthrough nausea requiring hydration, hospitalization or causing avoidable suffering.	Noted.
Richard	Merck	General	In reviewing this comparative effectiveness review, we have	Please see

Chapell			<p>identified three main issues that we believe must be addressed before the review can be finalized. We will discuss these concerns, with appropriate evidence to support them, and suggest ways to address them, in the relevant fields of the comment form. They are:</p> <p>1: In discussing the applicability of the available comparative data to patients over the age of 65, the EPC ignores the results of its own analysis as well as directly relevant data that have been made available to it. Ignoring relevant data can lead to erroneous conclusions, which can in turn lead to healthcare decisions that may not be clinically appropriate for patients.</p> <p>2: Some of the data considered by the EPC comes from studies conducted early in the development of aprepitant. These studies used formulations and dosages that were subsequently abandoned in favor of more effective forms. Data from studies using formulations that are not approved by the FDA or commercially available should not be used to influence healthcare decisions involving current clinical practice</p> <p>3: Section heads are unclear. Often, the reader cannot easily determine which comparisons include aprepitant and which do not.</p>	<p>responses to individual issues below.</p>
Mike Neuss	American Society of Clinical Oncology	Key Questions	<p>In the draft TA referenced above, AHRQ posed several key questions. One of these questions compared regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy to regimens given for longer periods of time. Based on the findings from two trials, the TA concludes that moderate strength evidence suggested that regimens containing aprepitant treatment on days two through four did not provide statistically significant improvement in complete response (RR, 1.22; 95% CI, 0.82 to 1.84) during the delayed period, and also that, two trials provided moderate strength evidence that regimens continuing aprepitant treatment on days two through four did not provide statistically significant improvement in complete response or no nausea compared with treatment regimens using aprepitant on day one only. We believe that the available evidence does not support such conclusions, as explained below.</p>	<p>Removed Herrington 2008, as both regimens were within 48-hour limit. Downgraded strength of evidence to insufficient due to use of unavailable formulation/dose of aprepitant in Navari 1999</p>

Mike Neuss	American Society of Clinical Oncology	Key Questions		
Mike Neuss	American Society of Clinical Oncology	Key Questions	First, AHRQ considered two trials for this key question. The first trial [Herrington, Cancer, 2008] did not stratify patients by known risk factors for chemotherapy-induced nausea and vomiting (CINV), and the use of highly emetogenic chemotherapy (i.e., cisplatin) was higher in the 3-day aprepitant arm. This study did not report the outcome of total control. The second trial considered for this question [Navari, NEJM, 1999] used doses of aprepitant that are considerably higher than the current FDA-approved doses (400mg on day 1 followed by 300mg on days 2-5, compared to 125mg on day 1 followed by 80mg on days 2-3).	See above response
Richard Chapell	Merck	Executive Summary	For the most part, the Executive summary is clear and well-written. The addition of some section headings to distinguish comparisons between two-drug regimens and comparisons between regimens with and without aprepitant would make it more clear. For example, after "Comparison of Oral Regimens" at the bottom of page six, please add a lower-level subhead saying "Comparison of 3-drug oral regimen with aprepitant and 2-drug oral regimen without aprepitant".	Added subheadings consistent with Results
Richard Chapell	Merck	Executive Summary	Then, before the first full paragraph on page 7, add a subheading saying "Comparison of two-drug regimens containing granisetron and two-drug regimens containing ondansetron."	Added subheadings consistent with Results
Richard Chapell	Merck	Executive Summary	Similarly, after "Comparison of mixed oral and injectable regimens", please add a subheading saying "Comparison of 3-drug oral regimen with aprepitant and 2-drug oral regimen without aprepitant."	Added subheadings consistent with Results
Richard Chapell	Merck	Executive Summary	Then, before the paragraph beginning "Based on low-to-moderate strength evidence?" add a subheading specifying the comparison being made, which is not clear from the text.	Added subheadings consistent with Results
Richard Chapell	Merck	Executive Summary	Please continue adding subheadings before every comparison throughout both the executive summary and the main document to ensure that it is completely clear which comparisons are being	Following peer review and public comment review,

			discussed.	conclusions changed as described above and below.
Richard Chapell	Merck	Executive Summary	<p>As discussed under Results, we disagree with several of the conclusions presented in the Executive Summary. Any changes made in response to our comments under Results should be reflected here as well. Specifically, we believe that the following statements should be removed or revised:</p> <p>"Additionally, the applicability of the evidence to patients age 65 and older needs to be determined."</p> <p>"Moderate strength evidence suggested that regimens continuing aprepitant treatment on days two through four did not provide statistically significant improvement in complete response (RR, 1.22; 95% CI, 0.82 to 1.84) during the delayed period."</p> <p>Please see our comments on results for the reasons behind these requests.</p>	Revised following addition of new evidence – see below.
Richard Chapell	Merck	Executive Summary	<p>The following statement is unclear and confusing "Based on low-to-moderate strength evidence, statistically significant differences in complete acute response between mixed oral and injectable regimens (RR, 1.00; 95% CI, 0.88 to 1.13) and either all-injectable or other mixed oral and injectable regimens (RR, 0.97; 95% CI, 0.88 to 1.07) were not evident. Evidence was insufficient to draw conclusions regarding other outcomes." Please state explicitly which regimens are being discussed and whether or not the comparison includes a treatment group receiving aprepitant. We believe it is important to always clearly distinguish when regimens containing aprepitant are - or are not - being discussed</p>	Revised following addition of new evidence – see below.
Richard Chapell	Merck	Executive Summary	<p>The following statement is not supported by the evidence presented in the review: "The likelihood is low that the findings reported above are broadly applicable to patients age 65 and older." The EPC has documented a perceived lack of evidence</p>	Following addition of unpublished data from Merck and a

			regarding patients over the age of 65. If this is the case, then there is no evidence with which to assess likelihood, and no conclusion regarding the applicability of the findings of the review to the patients over the age of 65 can be reached. We request that this statement be removed due to lack of evidence to support it.	pooled analysis of 2 trials, these conclusions have changed. Please see the final text.
Richard Chapell	Merck	Executive Summary	In any case, the EPCs conclusion in the Executive Summary contradicts the conclusion presented on page 31 of the review, which states that "Based on these studies, we can only presume that the effects (that aprepitant containing regimens were superior to regimens without aprepitant and no difference was found between 5-HT3 + corticosteroid regimens) are the same across age groups. The strength of this evidence is low, and further studies are highly likely to change these findings." If this conclusion remains in the final version of the review, it should be reflected in the Executive Summary.	Agree, the final conclusions of the report are now reflected in the executive summary.
Richard Chapell	Merck	Executive Summary	However, we believe the EPC's perception that there is little evidence available regarding patients over the age of 65 is incorrect, as we discuss in the results section. We will present clinical evidence from four randomized, controlled trials on the effectiveness of aprepitant on patients over the age of 65 and we will ask the EPC to review and discuss that evidence and include their conclusions about the evidence in both the results section and the executive summary.	Following addition of unpublished data from Merck and a pooled analysis of 2 trials, these conclusions have changed. Please see the final text.
Richard Chapell	Merck	Introduction/Background	Page 14: The report states that "This technology assessment report builds upon previous work conducted by the Oregon EPC? for the Drug Effectiveness Review Project (DERP)." During the preparation of that report, Merck & Co., Inc. supplied to DERP data from subgroup analyses of clinical trials that included patients over and under the age of 65. As patients over 65 are of particular interest to CMS, we find it surprising that the EPC chose not to include this data in the current review. We strongly request that it be included before the review is finalized.	While data were submitted previously, the comparisons being made in this report differ from those in the DERP report enough to make those submissions not useful here.

Richard Chapell	Merck	Results	As discussed in detail in our comments on the executive summary, throughout the document, section headers are a bit confusing. We request that headers specify more clearly each comparison under discussion.	Added subheadings consistent with Results
Richard Chapell	Merck	Results	Page 27: The text states that p-values were not provided for some quality of life outcomes. We apologize for the omission, and present them below. Please add these p-values to the discussion of quality of life for these studies. In the study by Hesketh et al (Reference 33) the numbers of patients reporting no significant impact of chemotherapy-induced nausea and vomiting on quality of life was 188 out of 254 (74.0%) in the aprepitant-treated group, compared to 162/252 (64.3%) in the standard care group. The difference between groups was statistically significant (p<0.05). In the study by Poli-Bigelli et al (Reference 35) the numbers of patients reporting no significant impact of chemotherapy-induced nausea and vomiting on quality of life was 189 out of 253 (74.7%) in the aprepitant-treated group, compared to 162/255 (63.5%) in the standard care group. The difference between groups was statistically significant (p<0.01).	We thank the reviewer for the supplemental data, which we used to calculate pooled RR's (95% CI's)
Richard Chapell	Merck	Results	Page 29: There appear to be referencing errors in the discussion of Question 1C. The two studies under discussion appear to be those by Herrington et al (Reference 21) and Navari et al. (Reference 34), while the text also refers to references 42 and 29. Please ensure that references are correct and that data was correctly entered into the analysis.	Corrected
Richard Chapell	Merck	Results	Page 29: We do not believe that the study by Navari et al. (Reference 34), is relevant for addressing Question 1C. In this study, an older formulation of aprepitant was used which is significantly different from the formulation used in subsequent trials and approved for use in clinical practice.	See above response
Richard Chapell	Merck	Results	Page 28, line 6: Typo: "lin"	Corrected
Richard Chapell	Merck	Results	The formulation used in the Navari trial was a tablet with a ~5m drug particle size. This compares to the marketed nano-particle formulation with <150 nm particle size and taken in capsule form (a >33 fold difference) used in the later trials. This nanoparticle	See above response

			formulation was developed because, when administered in the fasting state, it provides higher plasma concentrations than the 3 different formulations used earlier in the development process and it provides less variability in plasma concentrations when administered with food.	
Richard Chapell	Merck	Results	Using data from a study of a formulation that was abandoned in favor of a more effective formulation does not enable one to draw conclusions about the more effective formulation now in clinical use.	See above response
Richard Chapell	Merck	Results	Moreover, the dosing of oral aprepitant used in the Navari trial was significantly different from the dosing schedule used in subsequent trials and approved for use in clinical practice. The dosing was different, in terms of a 2-3 fold difference in dosage per day (when adjusted for differences in bioavailability between formulations) and in duration of use (days 1-3 vs. Days 1-5). Because of these differences between conditions in the trial and conditions of modern clinical practice, we believe that this study fails to meet EPC (and GRADE Working Group) criteria for "Directness".	See above response
Richard Chapell	Merck	Results	For this reason, we believe that the Navari trial should not be considered with regard to Question 1C, and the strength of evidence supporting the conclusions to Question 1C be downgraded from "Moderate" to, at best, "Low".	See above response
Richard Chapell	Merck	Results	Page 31: The question of whether the results of this review can be applied patients over the age of 65 is of special interest to the agency contracting for this technology assessment. For this reason it is important that all available evidence be considered when addressing the issue. The EPC has not considered evidence that had previously been made available to it during the DERP review process. Further, it has not considered the results of a good quality review assessing subgroup data in two previously published trials. This review, by Hesketh et al. (Supportive Care in Cancer; published first online September 2009) assesses subgroup analyses conducted as part of two trials discussed in the current AHRQ review. The trials are Hesketh et al., 2003 (Reference 33) and Poli-Bigelli et al., 2003 (Reference 35).	After consultation with AHRQ, these data have been used in the Final report. An appendix of these data is now included in the report as well.

			<ul style="list-style-type: none"> <li>• The review found that younger age is associated with a greater risk of chemotherapy-induced nausea and vomiting, but that aprepitant reduces risk of this outcome to the same extent among patients younger than age 65 and among those older than age 65. That is, aprepitant reduced the risk of chemotherapy-induced nausea and vomiting regardless of the presence or absence of risk factors for this outcome. We urge the EPC to examine this review and incorporate its findings into the final version of its document.</li> <li>• Examination of data from the same two studies (Hesketh et al., 2003 and Poli-Bigelli et al., 2003) led the US FDA to conclude that "No overall differences in safety or effectiveness were observed between these subjects [Those over the ages of 65 or 75] and younger subjects." This observation has been incorporated into the FDA-approved product label.</li> <li>• The subgroup analyses supporting this wording in the product label were conducted a priori as part of the planned protocols of the two studies. The results of these analyses were not published for reasons of space, but were shared with the EPC as part of their DERP review. We present them once again here and urgently request that the EPC incorporate them into their review.</li> </ul>	
Richard Chapell	Merck	Results	<p>Continued...In the study published by Hesketh et al., (2003; Reference 33), patients ranged in age from 18 to 84. Patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. There were 520 patients with evaluable data in the intent to treat population. Of these, there were 182 patients aged 65 or over, and 30 aged 75 or over.</p> <ul style="list-style-type: none"> <li>▪ In the Aprepitant group, there were 260 patients, of whom: <ul style="list-style-type: none"> <li>• 98 were age 65 or over, 79 (80.6%) of these had a complete response to antiemetic therapy.</li> <li>• 162 were under age 65, 110 (67.9%) of these had a complete response to antiemetic therapy.</li> <li>• 17 were age 75 or over, 16 (94.1%) of these had a</li> </ul> </li> </ul>	After consultation with AHRQ, these data have been used in the Final report. An appendix of these data is now included in the report as well.



			<p>complete response to antiemetic therapy.</p> <ul style="list-style-type: none"> <li>• 243 were under age 75, 173 (71.2%) of these had a complete response to antiemetic therapy.</li> <li>▪ In the Control group, there were 260 patients, of whom: <ul style="list-style-type: none"> <li>• 84 were age 65 or over, 50 (59.5%) of these had a complete response to antiemetic therapy.</li> <li>• 176 were under age 65, 86 (48.9%) of these had a complete response to antiemetic therapy</li> <li>• 13 were age 75 or over, 9 (69.2%) of these had a complete response to antiemetic therapy</li> <li>• 247 were under age 75, 127 (51.4%) of these had a complete response to antiemetic therapy</li> <li>• "Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate (p value not recorded).</li> </ul> </li> </ul>	
Richard Chapell	Merck	Results	<p>Continued...In the study published by <b>Poli-Bigelli et al.</b>, (2003; Reference 35), patients ranged in age from 18 to 82. Patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. There were 523 patients with evaluable data in the intent to treat population. Of these, there were 129 patients aged 65 or over, and 21 aged 75 or over.</p> <ul style="list-style-type: none"> <li>▪ In the Aprepitant group, there were 260 patients, of whom: <ul style="list-style-type: none"> <li>• 65 were age 65 or over, 45 (69.2%) of these had a complete response to antiemetic therapy.</li> <li>• 195 were under age 65, 118 (60.5%) of these had a complete response to antiemetic therapy.</li> <li>• 11 were age 75 or over, 9 (81.8%) of these had a complete response to antiemetic therapy.</li> <li>• 249 were under age 75, 154 (61.8%) of these had a complete response to antiemetic therapy.</li> </ul> </li> <li>▪ In the Control group, there were 263 patients, of whom:</li> </ul>	<p>After consultation with AHRQ, these data have been used in the Final report. An appendix of these data is now included in the report as well.</p>

			<ul style="list-style-type: none"> <li>• 64 were age 65 or over, 30 (46.9%) of these had a complete response to antiemetic therapy.</li> <li>• 199 were under age 65, 84 (42.2%) of these had a complete response to antiemetic therapy.</li> <li>• 10 were age 75 or over, 5 (50.0%) of these had a complete response to antiemetic therapy.</li> <li>• 253 were under age 75, 109 (43.1%) of these had a complete response to antiemetic therapy.</li> </ul> <p>"Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate (p value not recorded).</p>	
Richard Chapell	Merck	Results	<p>In addition to the two studies on which the FDA and Hesketh (2009) based their conclusions, at least two other clinical trials meeting EPC inclusion criteria included a priori analyses of the effect of age on complete response, the results of which were not published. We present them here, and request that the EPC include them in their final analysis.</p> <ul style="list-style-type: none"> <li>• In the study by Warr et al., 2005 (Reference 27), patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. Patient ages ranged from 23 to 78 years. There were 857 patients with evaluable data in the intent to treat population. Of these, there were 129 patients aged 65 or over, and 19 aged 75 or over. <ul style="list-style-type: none"> <li>○ In the Aprepitant group, there were 433 patients, of whom: <ul style="list-style-type: none"> <li>▪ 69 were age 65 or over, 42 (60.9%) of these had a complete response to antiemetic therapy.</li> <li>▪ 364 were under age 65, 178 (48.9%) of these had a complete response to antiemetic therapy.</li> <li>▪ 12 were age 75 or over, 9 (75.0%) of these had a complete response to antiemetic therapy.</li> <li>▪ 421 were under age 75, 211 (50.1%) of these had a complete response to antiemetic therapy.</li> </ul> </li> <li>○ In the Control group, there were 424 patients, of whom: <ul style="list-style-type: none"> <li>▪ 60 were age 65 or over 33 (55.0%) of these had a</li> </ul> </li> </ul> </li> </ul>	<p>After consultation with AHRQ, these data have been used in the Final report. An appendix of these data is now included in the report as well.</p>

- complete response to antiemetic therapy.
- 364 were under age 65, 147 (40.4%) of these had a complete response to antiemetic therapy.
  - 7 were age 75 or over, 4 (57.1%) of these had a complete response to antiemetic therapy
  - 417 were under age 75, 176 (42.2%) of these had a complete response to antiemetic therapy.
  - "Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate between patients aged 65 and over and patients who were less than 65 years old ( $p=0.788$ ) or between patients aged 75 and over and patients who were less than 75 years old ( $p=0.631$ ).
  - In the study published by Schmoll et al., (2006; Reference 36), patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. Patients ranged in age from 20 to 82. There were 484 patients with evaluable data in the intent to treat population. Of these, there were 156 patients aged 65 or over, and 15 aged 75 or over.
    - In the Aprepitant group, there were 243 patients, of whom:
      - 80 were age 65 or over 63 (78.8%) of these had a complete response to antiemetic therapy.
      - 163 were under age 65, 112 (68.7%) of these had a complete response to antiemetic therapy.
      - 9 were age 75 or over 7 (77.8%) of these had a complete response to antiemetic therapy.
      - 234 were under age 75, 168 (71.8%) of these had a complete response to antiemetic therapy.
    - In the Control group, there were 241 patients, of whom:
      - 76 were age 65 or over, 53 (69.7%) of these had a complete response to antiemetic therapy.
      - 165 were under age 65, 93 (56.4%) of these had a

			<p>complete response to antiemetic therapy.</p> <ul style="list-style-type: none"> <li>○ 6 were age 75 or over, 3 (50.0%) of these had a complete response to antiemetic therapy.</li> <li>○ 235 were under age 75, 143 (60.9%) of these had a complete response to antiemetic therapy.</li> <li>○ "Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate between patients aged 65 and over and patients who were less than 65 years old (p=0.919) or between patients aged 75 and over and patients who were less than 75 years old (p=0.612).</li> </ul>	
Richard Chapell	Merck	Results	We apologize for the format of these data as presented here, but the nature of the stakeholder comment process makes it impossible to include attachments or to paste tables into these comments. We would be glad to supply these data in more accessible form as well as supply any other information the EPC finds necessary to fully address this issue. Please contact us if further information is desired.	Noted.
Richard Chapell	Merck	Results	In light of this additional data, we request that the EPC reassess its conclusions as to whether the results of the review can be applied to patients over the age of 65.	In light of the submitted evidence, the conclusions have changed. See Final report.
Richard Chapell	Merck	Discussion/Conclusion	Page 34: "Additionally, little evidence was available for evaluating disparate effects on age, gender, socioeconomic status, or ethnicity/race." We have provided additional evidence demonstrating that there are no disparate effects of age. Please reevaluate this statement in light of this evidence.	See above.
Richard Chapell	Merck	Discussion/Conclusion	Page 34: "In order to determine the comparative benefits and harms of antiemetic regimens in adults aged 65 and older who are receiving emetogenic chemotherapy or radiation therapy, larger trials are warranted. Such trials should target broader age ranges and include a priori plans to conduct subgroup analyses based on age or specifically enroll patients aged 65 and older."	These suggestions for future research have been modified in light of new evidence

			A priori subgroup analyses have been performed. Please revise this statement to acknowledge this fact.	– as the commenter points out <i>a priori</i> subgroup analyses have been done on age. However, considering the lack of evidence on harms, outcomes other than complete response, and comparing other regimens we continue to recommend additional research in patients 65 and over is needed.
Richard Chapell	Merck	Tables	Changes made in response to our comments under Results should be reflected in Tables 8 through 10 as well as the Executive Summary.	Done
Richard Chapell	Merck	Figures	Labeling on many of the forest plots presented in the document is unclear. Please ensure that the labels indicating whether a response favors one treatment group or another are evenly distributed on either side of the point indicating no difference. Otherwise, graphs could easily be misinterpreted.	Labels added

<sup>1</sup> Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.

<sup>2</sup> Affiliation is labeled "NA" for those who did not disclose affiliation.

<sup>3</sup> If listed, page number, line number, or section refers to the draft report.

<sup>4</sup> If listed, page number, line number, or section refers to the final report.