Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Overview of CDR Clinical and Pharmacoeconomic Reports

CDR

May 2008

Aprepitant
Emend™ — Merck Frosst Canada Ltd.
Indication — Chemotherapy-induced Nausea and Vomiting

Supporting Informed Decisions

À l'appui des décisions éclairées

Cite as: Common Drug Review*. Aprepitant (Emend™ — Merck Frosst Canada Ltd.), Indication — Chemotherapy-induced Nausea and Vomiting: Overview of CDR Clinical and Pharmacoeconomic Reports* [May 2008]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.

Production of this overview is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

CADTH takes sole responsibility for the final form and content of this overview. The statements, conclusions and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

Canadian Agency for Drugs and Technologies in Health (CADTH)
600-865 Carling Avenue, Ottawa, ON, Canada K1S 5S8
Telephone: (613) 226-2553, Fax: (613) 226-5392
www.cadth.ca

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

Overview of CDR Clinical and Pharmacoeconomic Reports

Aprepitant

Emend™ — Merck Frosst Canada Ltd.

Indication – Chemotherapy-induced Nausea and Vomiting

May 2008

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
HEC	highly emetogenic chemotherapy
MEC	moderately emetogenic chemotherapy
NNT	number needed to treat
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale
5-HT$_3$	5-hydroxytryptamine

REVIEW IN BRIEF

Aprepitant (Emend™) — CEDAC Final Recommendation Issued February 20, 2008

Aprepitant (Emend) was submitted by the manufacturer to the Common Drug Review (CDR) for consideration for formulary listing by participating public drug plans. This Review in Brief includes the Canadian Expert Drug Advisory Committee's (CEDAC) recommendation and reasons for recommendation, and information used by CEDAC in making its recommendation including: a summary of the best available clinical and pharmacoeconomic evidence identified and reviewed by the CDR, as well as information submitted by the manufacturer.

CEDAC Recommendation

CEDAC recommended that aprepitant, when used in combination with a 5-HT_3 antagonist and dexamethasone, be listed for the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy (e.g., cisplatin >70 mg/m^2) in patients who have experienced emesis, despite treatment with a combination of a 5-HT_3 antagonist and dexamethasone, in a previous cycle of highly emetogenic chemotherapy (HEC).

Reasons for the Recommendation

- In patients receiving HEC, aprepitant has been shown to reduce the number of patients experiencing emesis, but it has not been consistently shown to reduce nausea.
- In patients receiving HEC, the incremental cost-effectiveness of aprepitant is highly sensitive to whether one or four days of a 5-HT_3 antagonist was used, ranging from $21,000 to $101,000 per quality-adjusted life year (QALY). Given this uncertainty, the Committee felt that aprepitant should be reserved for use in patients who have not responded to a combination of a 5-HT_3 antagonist and dexamethasone.
- Aprepitant has not been shown to be cost-effective in patients receiving moderately emetogenic chemotherapy (MEC).

Drug

- Aprepitant is an orally administered neurokinin-1 receptor antagonist.
- Aprepitant, when used in combination with a 5-HT_3 antagonist class of antiemetics and dexamethasone, is approved by Health Canada for the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy and for the prevention of nausea and vomiting in women due to treatment with moderately emetogenic cancer chemotherapy consisting of cyclophosphamide and an anthracycline.
- Aprepitant is available in 80 mg and 125 mg capsules. The recommended dosing regimen is 125 mg one hour before chemotherapy (day one) and 80 mg once daily in the morning on day two and three.

Condition

Chemotherapy-induced nausea and vomiting (CINV) can be acute, delayed, or anticipatory. Acute CINV occurs in the first 24 hours after administration of chemotherapy. Delayed CINV occurs more than 24 hours after administration of chemotherapy; it peaks at approximately 48 to 72 hours and can last up to 96 hours. Anticipatory CINV is a learned response following the experience of nausea and/or vomiting during a previous episode of chemotherapy. Current treatment of CINV includes 5-HT_3 receptor antagonists and dexamethasone.

Clinical Review

- A systematic review of double-blind randomized controlled trials (RCTs) in adult patients receiving HEC or adult female patients receiving MEC, consisting of cyclophosphamide and an anthracycline, was undertaken.
- Four double-blind, randomized, placebo-controlled trials met the inclusion criteria for the systematic review, three in patients receiving HEC and one in women receiving MEC.
- In all trials, aprepitant or placebo was added to treatment with ondansetron (a 5-HT_3 antagonist) and dexamethasone on day one and was continued on day two and three.

- The control arms of the RCTs consisted of treatment with dexamethasone and ondansetron, with treatments extended for up to four days.
- Outcomes were reported as acute (within the first 24 hours of chemotherapy), delayed (>24 hours after chemotherapy) or overall (during day one to five).

Results

- The primary outcome of all four trials was complete response in the overall phase – a composite endpoint defined as no emesis and no rescue therapy during the five days following chemotherapy.

HEC

- Aprepitant resulted in statistically significant improvements in complete response during the acute, delayed, and overall phase, in all three trials.
- All three trials reported statistically significant reductions in favour of aprepitant in the number of patients with emesis during the acute phase, delayed phase, and overall. Aprepitant did not consistently reduce nausea.
- Of the two trials that assessed health-related quality of life outcomes, the number of patients reporting that CINV had no impact on daily life was significantly higher in the aprepitant group.
- Two of the three trials reported statistically significant differences in favour of aprepitant in the number of patients who required rescue therapy during the acute phase, delayed phase, or overall.

MEC

- Women receiving aprepitant experienced fewer episodes of emesis during the acute phase, delayed phase, and overall
- There were no statistically significant differences between the groups in the use of rescue therapy during any phase, or in the number of patients who experienced no nausea overall.

Adverse Events

- There were no significant differences between aprepitant and placebo in serious adverse events, treatment-related adverse events, or withdrawals due to adverse events.
- Aprepitant should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4 and CYP2C9, including chemotherapy agents, as it causes inhibition of CYP3A4 and induction of CYP2C9.

Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

Highlights

- Aprepitant costs $90.54 for a three-day course of therapy.

HEC

- Based on the clinical trials, the cost of an antiemetic regimen including aprepitant is $201 compared to a regimen without aprepitant at $115 to $169 (depending on the regimen used).
- The manufacturer, in the submitted economic evaluation, reports a cost per QALY of $21,000 for the addition of aprepitant to a regimen that uses a 5-HT_3 antagonist through the delayed phase.
- The cost per QALY increases to $101,300 if the 5-$HT_3$ antagonist is used only on day one of chemotherapy.

MEC

- The addition of aprepitant to an antiemetic regimen increases the cost from $57 to $110.
- The manufacturer, in the submitted economic evaluation, reports a cost per QALY of $126,500 for the addition of aprepitant, assuming the use of a 5-HT_3 antagonist through the delayed phase.
- The cost per QALY increases to $220,000 if the 5-$HT_3$ antagonist is used only on day one of chemotherapy.

What is the CDR?

The CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

OVERVIEW

Context

This document is an overview of two Common Drug Review (CDR) reports: the CDR Clinical Review Report (a systematic review of the clinical evidence) and the CDR Pharmacoeconomic Review Report (a critique of the submitted pharmacoeconomic evaluation). These reports were prepared by the CDR Directorate to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that the CDR Directorate has identified and compiled, including that submitted by the manufacturer.

This overview is based on the aprepitant CDR Clinical Review Report, 52 pages in length with 51 references, and the aprepitant CDR Pharmacoeconomic Review Report, 20 pages with nine references. The manufacturer had the opportunity to provide feedback on each of the full reports and on this Overview. The CDR Directorate has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information, as defined in the CDR Confidentiality Guidelines, may have been used in the preparation of these documents and thus, considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

Introduction

Aprepitant (Emend™) is an orally administered neurokinin-1 (NK1) receptor antagonist. The drug, in combination with a 5-HT_3 antagonist class of antiemetics and dexamethasone, is indicated for:

- The prevention of acute and delayed nausea and vomiting due to highly emetogenic chemotherapy (HEC), and
- The prevention of nausea and vomiting in women due to treatment with moderately emetogenic cancer chemotherapy (MEC) consisting of cyclophosphamide and anthracycline.

Aprepitant is available in 80 mg and 125 mg capsules. The recommended dosing regimen is 125 mg one hour before chemotherapy on treatment day one and 80 mg once daily on day two and three.

Chemotherapy-induced nausea and vomiting (CINV) can be acute, delayed or anticipatory.[1-3] Acute CINV occurs in the first 24 hours after administration of chemotherapy. Delayed CINV occurs more than 24 hours after administration of chemotherapy; it peaks at approximately 48 to 72 hours and can last up to 96 hours. Anticipatory CINV is a learned response following the experience of nausea and/or vomiting during a previous episode of chemotherapy.

Therapy for CINV includes the inhibition of the dopamine, 5-HT_3, and more recently, NK1 receptors, as well as the use of corticosteroids. The older dopamine receptor antagonists include prochlorperazine, metoclopramide, and haloperidol. These agents, while important, have limited efficacy and/or high toxicities.[3] The 5-HT_3 antagonists are generally considered the most useful class of antiemetic agents for the prevention of acute CINV. Their use in delayed CINV is more controversial.[4] The 5-HT_3 antagonists available in the Canadian market include:

ondansetron, granisetron, and dolasetron. Dexamethasone is the most widely used corticosteroid for CINV. It is used alone when chemotherapy of low emetogenic potential is administered, and either alone or in combination with other agents for the prevention of acute or delayed CINV for moderate and highly emetogenic chemotherapy (HEC).[5] The NK1 receptor antagonists are the newest pharmacologic class of antiemetics, with aprepitant being the first available.

Clinical Review

Objective

To evaluate the effect of aprepitant on patient outcomes compared with standard therapies and placebo in male or female adult patients scheduled to receive HEC, or female adult patients scheduled to receive MEC consisting of cyclophosphamide and an anthracycline.

Methods

For information on the methodology employed in the full CDR Clinical Review of aprepitant refer to Appendix I.

Selection Criteria

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

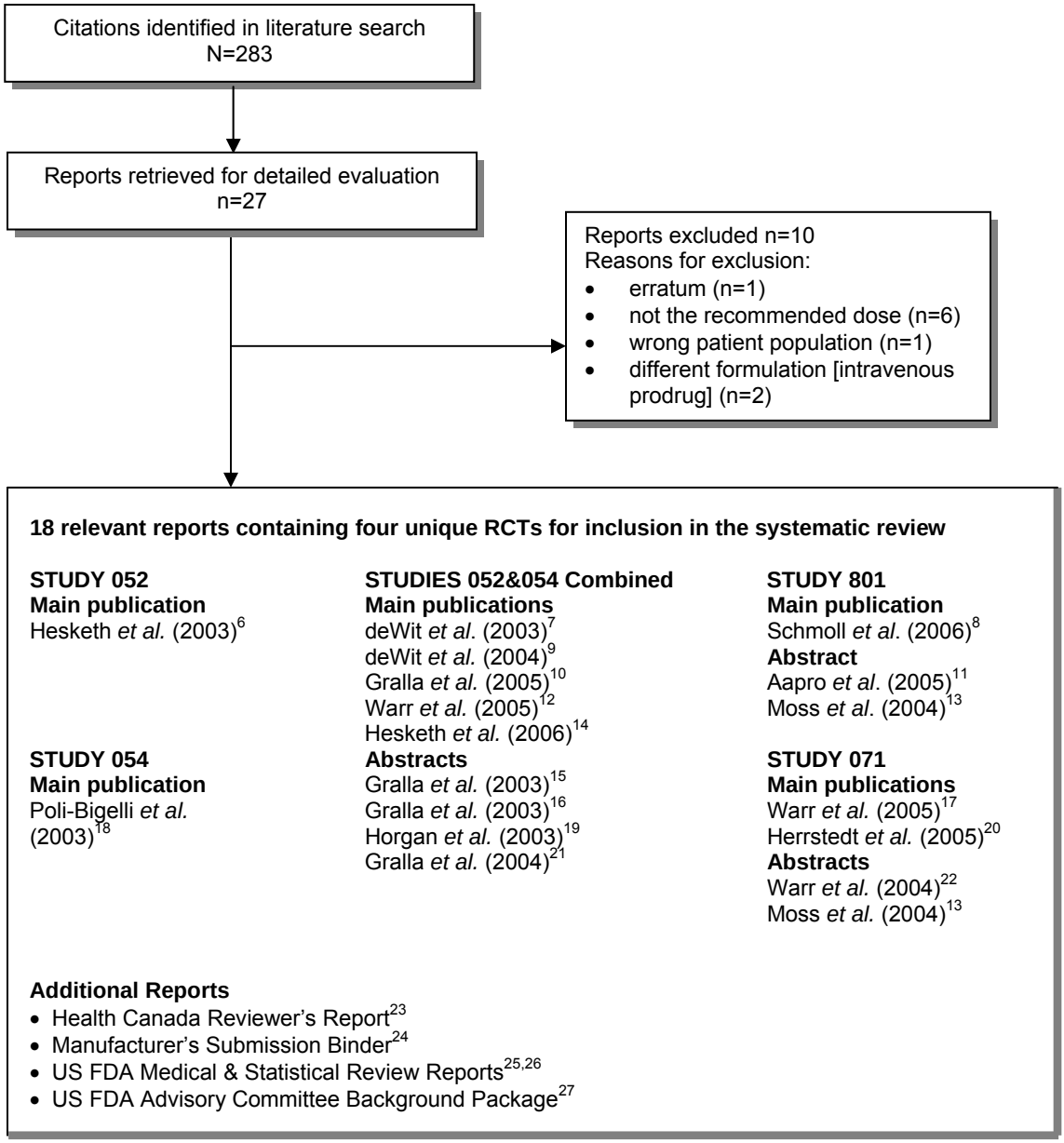
Table 1: Selection Criteria				
Clinical Trial Design	**Patient Population**	**Interventions**	**Appropriate Comparators***	**Outcomes**
Published and unpublished double-blind RCTs	Male or female patients (≥18 years of age) who are scheduled to receive HEC OR female patients (≥18 years of age) who are scheduled to receive MEC consisting of cyclophosphamide and anthracycline. Subpopulations: Patients who have had an inadequate response or intolerance to previous standard antiemetic therapy.	Oral aprepitant (Emend) capsules for three consecutive days: 125 mg on day one, and 80 mg daily on day two and three, in combination with a 5-HT_3 antagonist (ondansetron, granisetron, dolasetron) and dexamethasone	Standard therapy: • Corticosteroid and/or a 5-HT_3 antagonist (ondansetron, granisetron, dolasetron)	• Total control (no emesis, no nausea, and no rescue therapy)† • Complete protection (no emesis, no significant nausea, and no rescue therapy)† • Complete response (no emesis and no rescue therapy)† • No nausea† • No significant nausea† • No vomiting† • No rescue therapy† • Severity of nausea† • SAEs • Impact on chemotherapy regimen • Lack of response (non-responders) • QoL as assessed by any valid method • WDAEs • AEs

AE=adverse event; HEC=highly emetogenic chemotherapy; MEC=moderately emetogenic chemotherapy; QoL=quality of life; RCT=randomized controlled trial; SAE=serious adverse event; WDAE=withdrawal due to adverse event.
*Standard therapies available in Canada (may include drug or non-drug interventions)
†In the acute (day one), and/or delayed (day two to five), and/or overall (day one to five) phase.

Results

Findings from the Literature

Figure 1: QUOROM Flowchart Detailing Flow of Studies



Summary of Evidence

Included Studies and Trial Characteristics

Four multi-centre, double-blind, parallel-group RCTs were included: studies 052[6] (n=530), 054[18] (n=569), 801[8] (n=489), and 071[17] (n=866). The medication regimens in the four studies are detailed in Table 2. Studies 052, 054, and 801 enrolled patients commencing their first cycle of HEC with cisplatin. They evaluated the addition of aprepitant to an antiemetic regimen consisting of ondansetron and dexamethasone. While there are some outcome data available beyond cycle 1, all three trials of HEC were designed to evaluate the efficacy of aprepitant for only the initial cycle of chemotherapy. Studies 052 and 054 were designed to be identical, a priori, to allow subsequent pooling of data for analysis. Study 801 differed from the 052 and 054 trials in that ondansetron was used from day two to four of the standard therapy arm. Study 071 evaluated aprepitant in breast cancer patients undergoing MEC with cyclophosphamide and an anthracycline during four cycles of chemotherapy; analysis included all four cycles. In Study 071, aprepitant was examined as add-on therapy to ondansetron and dexamethasone on the day of chemotherapy, and compared with ondansetron on day two and three post-chemotherapy. All trials allowed patients to take rescue therapy. All RCTs were large and well-designed.

Table 2: Medication Regimens by Study

Study	Day one		Day two to three		Day four	
	APR Arm	Standard Therapy	APR Arm	Standard Therapy	APR Arm	Standard Therapy
Study 052 and 054 (HEC)	PO APR 125 mg IV OND 32 mg PO DEX 12 mg	IV OND 32 mg PO DEX 20 mg	PO APR 80 mg once daily PO DEX 8 mg once daily	PO DEX 8 mg twice daily	PO DEX 8 mg	PO DEX 8 mg twice daily
Study 801 (HEC)	PO APR 125 mg IV OND 32 mg PO DEX 12 mg	IV OND 32 mg PO DEX 20 mg	PO APR 80 mg once daily PO DEX 8 mg once daily	PO OND 8 mg twice daily PO DEX 8 mg twice daily	PO DEX 8 mg	PO OND 8 mg twice daily PO DEX 8 mg twice daily
Study 071 (MEC)	PO APR 125 mg PO OND 8 mg twice daily PO DEX 12 mg	PO OND 8 mg twice daily PO DEX 20 mg	PO APR 80 mg once daily	PO OND 8 mg twice daily	—	—

APR=aprepitant; DEX=dexamethasone; HEC=highly emetogenic therapy; IV=intravenous; MEC=moderately emetogenic therapy; OND=ondansetron; PO=oral.

Summary of Results

For results from individual trials, refer to Table 3.

All results from the HEC trials are after one cycle of therapy.

HEC Trials (052, 054, 801)

- For Study 052, there was no difference between the aprepitant group and the control group in the number of patients with total control (no emesis, no nausea, and no rescue). For Study 054, the number of patients with total control was statistically significantly higher in the aprepitant group compared with the control group in the delayed CINV, but not in the acute phase. Study 801 did not evaluate this outcome.
- For all three HEC studies, the number of patients with a complete response (no emesis or rescue therapy) was statistically significantly higher in the aprepitant group compared with the control group for the acute, delayed, and overall CINV phases.

- For Study 052, there was no difference between the aprepitant group and the control group in the number of patients with no nausea [visual analogue scale (VAS)<5 mm on a 100 mm scale]. For Study 054, the number of patients with no nausea was statistically significantly higher in the aprepitant group compared with the control group in the delayed, but not in the acute phase. However, when studies 052 and 054 were pooled for analysis by the manufacturer, a statistically significant difference in this outcome was observed in favour of aprepitant for all three phases. Study 801 did not evaluate this outcome.
- For all three HEC studies, the number of patients with no vomiting was statistically significantly higher in the aprepitant group compared with the control group for all three phases.
- The number of patients needing rescue therapy was statistically significantly lower in the aprepitant group compared with the control group in studies 052 and 054, but not in Study 801.
- Studies 052 and 054 assessed QoL with the Functional Living Index Emesis (FLIE) questionnaire (Appendix II). The number of patients with an average FLIE score >6 (no impact of CINV on daily life) in the overall phase was statistically significantly higher in the aprepitant group compared with the control group.
- There were no statistically significant differences between treatment groups in withdrawals due to AEs, treatment-related AEs, serious AEs (SAEs), or death.

MEC Trial (071)

- The number of patients with a complete response (no emesis, no rescue) was statistically significantly higher in the aprepitant group compared with the control group in the acute and overall phases, but not in the delayed phase after one cycle of chemotherapy. The number of patients demonstrating a complete response in the overall phase was statistically significantly higher in the aprepitant group compared with the control group for all four cycles of chemotherapy.
- There were no statistically significant differences between the aprepitant group and the control group in the number of patients without any nausea in the overall phase for all four cycles.
- The number of patients with no vomiting was statistically significantly higher in the aprepitant group compared with the control group for all three phases after one cycle.
- There was no statistically significant difference between study groups in use of rescue therapy after cycle one.
- The number of patients with no impact of CINV on the QoL, as assessed with the FLIE questionnaire, was statistically significantly higher in the aprepitant group compared with the control group after one cycle (76% versus 64%, respectively, p<0.01).
- There were no statistically significant differences between treatment groups in withdrawals due to AEs, treatment-related AEs, or SAEs. No deaths occurred in Study 071.

Table 3: Summary of Trial Outcomes

Study Reference	Duration, Main Inclusion, # Sites, N	Total Control NNT (95% CI)	Complete Protection NNT (95% CI)	Complete Response NNT (95% CI)	No Nausea (VAS <5mm) NNT (95% CI)	No Significant Nausea (VAS<25mm) NNT(95% CI)	No Vomiting NNT(95% CI)	No Rescue Therapy NNT (95% CI)	QoL: FLIE* NNT (95% CI)
Study 052	1 cycle, high-dose CIS, 56 sites, N=530	acute: NS delayed: NS overall: NS	acute: 10 (6,30) delayed: 7 (4,15) overall: 7 (4,18)	acute: 9 (6,21) delayed: 5 (4,9) overall: 5 (4,8)	acute: NS delayed: NS overall: NS	acute: NS delayed: NS overall: NS	acute: 9 (6,22) delayed: 5 (3,7) overall: 4 (3,7)	acute: 19 (10,167) delayed: 13, (7,200) overall: 10 (6,37)	acute: NI delayed: NI overall: 10 (6, 59)
Study 054	1 cycle, high-dose CIS, 18 sites, N=569	acute: NS delayed: 6 (4,13) overall: 8 (5,23)	acute: 6 (4,13) delayed: 6 (3,12) overall: 7 (4,16)	acute: 7 (5,14) delayed: 5 (3,8) overall: 5 (4,9)	acute: NS delayed: 8 (5,23) overall: 10 (5,62)	acute: 13 (8,59) delayed: NS overall: NS	acute: 7 (5,13) delayed: 4 (3,7) overall: 5 (3,7)	acute: 16 (9, 48) delayed: 11 (6, 53) overall: 10 (6, 38)	acute: NI delayed: NI overall: 9 (5,31)
Study 801	1 cycle, high-dose CIS, 95 sites, N=489	NI	NI	acute: 12 (7,56) delayed: 9 (5,36) overall: 9 (5,32)	NI	NI	acute: 12 (7,50) delayed: 7 (4,15) overall: 7 (4,16)	acute: NS delayed: NS overall: NS	NI
Study 071	4 cycles, MEC in women with BC, 56 sites, N=866	NI	NI	acute: 14 (8, 91) delayed: NS overall: 12 (7, 59)	acute: NI delayed: NI overall: NS	acute: NI delayed: NI overall: NS	acute: 9 (6,16) delayed: 8 (6,16) overall: 6 (4,9)	acute: NS delayed: NS overall: NS	acute: NI delayed: NI overall: 13 (7,77)

BC=breast cancer; CI=confidence interval; CIS=cisplatin; FLIE=Functional Living Index–Emesis; MEC=moderately emetogenic chemotherapy; NI=outcome was not included in the trial; NNT=number needed to treat; NS=not statistically significant; QoL=quality of life; VAS=visual analogue scale.

*Number of patients with total FLIE score >6 or 7 (no impact on daily life).

Notes

- All efficacy outcomes, which were statistically significant, were in favour of the aprepitant regimen compared with the standard regimen.
- Total control=no emesis, no rescue, no nausea; complete protection=no emesis, no rescue, no significant nausea; complete response=no emesis, no rescue.
- Details of medication regimens are outlined in Table 2.
- Phases of CINV:[6]
  - Acute= within 24 hours of the start of chemotherapy.
  - Delayed= >24 hours after chemotherapy.
  - Overall= occurring during day one to five.

Discussion

Data from three large RCTs in patients receiving HEC indicated that the tested regimens, using aprepitant as an adjunctive agent, are more effective than the control regimens in reducing chemotherapy-induced vomiting, but did not consistently reduce nausea. Improvements in the measure of QoL, assessed by the FLIE questionnaire (Appendix II) were also observed in the regimens using aprepitant compared with the control regimens. In two of the three trials, the regimens using aprepitant were associated with a reduction in the use of rescue therapy, compared with the control regimens.

In a RCT of patients with breast cancer who were receiving MEC, the efficacy of the regimen using aprepitant versus the control regimen was not as large as it was in the HEC trials. There were consistent reductions in the rates of vomiting, but there was no reduction in use of rescue therapy in patients taking a regimen with aprepitant, compared with the control regimen. The regimen using aprepitant was associated with improvement in the measure of QoL, but did not reduce the number of patients experiencing nausea, compared with the control regimen.

Quality of Evidence

- All RCTs were large and well-designed studies.
- All employed a modified intent-to-treat analysis.
- External validity was limited because only the first cycle of chemotherapy was studied in three of the trials and results from the first cycle cannot necessarily be extrapolated to subsequent cycles. Other limitations were: HEC was confined to cisplatin, the only 5-HT_3 antagonist evaluated was ondansetron, and only chemotherapy-naïve patients were enrolled.
- Dexamethasone doses were adjusted in an attempt to offset the pharmacokinetic interaction between aprepitant and dexamethasone. Co-administration of aprepitant with dexamethasone has been shown to increase the 24-hour area under the concentration-time curve 2.2-fold[28] and in the included studies, the dose of dexamethasone on day one was only reduced by 40%. Potential confounding of results due to increased dexamethasone levels cannot be ruled out.

Efficacy

HEC Trials

- In studies 052 and 054, aprepitant was associated with a 22% reduction in vomiting and 10% reduction in the use of rescue therapy in the overall phase, relative to standard therapy. Aprepitant did not consistently reduce rates of nausea. The efficacy of aprepitant was less pronounced in study 801, with a 14% reduction in vomiting overall, and a non-significant reduction in the use of rescue therapy. These differences may be a result of differences in the standard therapy regimens between studies, with ondansetron being used on day two to four in study 801, but not in studies 052 and 054.
- Studies 052 and 054 observed a statistically significant improvement in the FLIE score for aprepitant compared with standard treatment. However, the 95% confidence interval (CI) around the QoL number need to treat (NNT) was wide, indicating low precision in these estimates.

MEC Trials

- In patients receiving MEC, aprepitant was associated with reductions in vomiting and improvements in QoL, but had no effect on nausea or on the use of rescue therapy.
- The lower efficacy of aprepitant observed in this trial, as compared with the results from the HEC trials, may be a result of reduced effectiveness of aprepitant for patients receiving MEC, lack of dexamethasone on day two to four, or gender differences between the MEC and HEC trials.

Harms

There were no significant differences in harms data between groups of patients receiving adjunctive aprepitant or a standard antiemetic treatment regimen.

Pharmacoeconomic Review

Context

The CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. The CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

Objective of the Manufacturer's Submitted Economic Evaluation

From the perspective of the public payer in Ontario, what is the cost-effectiveness of routine use of aprepitant in the prevention of CINV in patients receiving HEC or MEC compared with usual care?

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer conducted a cost-effectiveness and cost-utility analysis of aprepitant in combination with ondansetron and dexamethasone compared to a treatment regimen without aprepitant (ondansetron and dexamethasone alone) for the treatment of chemotherapy-induced nausea and vomiting (CINV). The economic model was used to run two analyses, one for patients receiving highly emetogenic chemotherapy (HEC) and another for those receiving moderately emetogenic chemotherapy (MEC).

The model structure was the same for both analyses: patients could experience acute emesis (within one day of chemotherapy) and/or delayed emesis (within two to five days of chemotherapy). Patients who did not develop emesis were further divided into those that experienced minimal or no nausea and those that experienced greater than minimal nausea. Patients were defined as complete responders if they did not experience emesis in either the acute or delayed phase and did not require rescue medication. The duration of the analysis was five days; consequently, costs and benefits were not discounted.

The treatment and comparator regimens were based on the clinical trials, study 0801 for HEC and study 071 for MEC. For the HEC model, clinical outcomes were derived from study 0801,[8] and resource utilization was derived from studies 052[6] and 054.[18] The MEC model derived the

clinical outcomes and resource utilization from study 071.[17] The utility estimates were obtained from a published Canadian study[29] and were used for both analyses.

Cost Comparison

CDR produced Tables 4, 5, and 6 to provide a comparison of the cost of treatment of the submitted drug with comparator treatments deemed appropriate by clinical experts.

Comparators may reflect recommended or actual practice. Comparators are not restricted to drugs but may include devices or procedures where appropriate. Costs are manufacturer list prices, unless otherwise specified.

Table 4: Cost Comparison of Aprepitant versus Comparator Treatments					
Drug / Comparator	**Strength**	**Dosage Form**	**Price ($)**	**Typical Dose**	**Average Cost per Course ($)**
Aprepitant (Emend)*	**80 mg 125 mg 2x80 mg/ 1x125 mg**	**cap cap Tri-Pack**	**30.1800 30.1800 90.5400**	**125 mg one hour before chemotherapy (day 1), and 80 mg once daily in the morning (days two and three)**	**$90.54**
5-HT$_3$ Antagonists					
Ondansetron (generic)	4 mg 8 mg	tab tab	5.9884 9.1402	8 mg pre-chemo then 8 mg every 8 hours for 24 to 48 hours *Highly emetogenic chemo*: (8 mg IV pre-chemo then) 8 mg every 8 hours for up to 5 days *Less emetogenic chemo*: 8 mg pre-chemo and 8 mg twice daily for up to 5 days	$27.42 to $54.84 $137.10 $91.40
Ondansetron (Zofran, Zofran ODT)	4 mg 8 mg 4 mg 8 mg 4 mg/5mL	tab tab ODT ODT O/L	12.7694 19.4851 12.7694 19.4851 1.9484	8 mg pre-chemo then 8 mg every 8 hours for 24 to 48 hours *Highly emetogenic chemo*: (8 mg IV pre-chemo) then 8 mg every 8 hours for up to 5 days *Less emetogenic chemo*: 8 mg pre-chemo and 8 mg twice daily for up to 5 days	$58.46 to $116.91 $292.28 $194.85
Granisetron (Kytril)	1 mg	tab	18.0000	2 mg pre-chemo then 1 mg 24 hours later OR 2 mg on the day of chemo	$54.00 $36.00
Dolasetron mesylate (Anzemet)	50 mg 100 mg	tab tab	13.7247 27.4493	200 mg pre-chemo then 100 mg to 200 mg 24 hours later 100 mg pre-chemo	$82.35 to $109.80 $27.45
Other Treatment Medications					
Nabilone (Cesamet)	0.5 mg 1 mg	cap cap	3.1026 6.2050	1 mg or 2 mg twice daily, first dose evening before chemo, 2nd dose 1 to 3 hours pre-chemo. If needed continue up to 24 hours post-chemo Maximum: 6 mg daily	$12.41 to $49.64
Dronabinol (Marinol)	2.5 mg 5 mg 10 mg	cap cap cap	1.9100 3.8200	2.5 mg to 10 mg every 4 to 12 hours† Maximum: 6 doses daily	$11.46 to 15.28
Dexamethasone (generics)	0.5 mg 0.75 mg 4 mg	tab tab tab	0.1564 0.4883 ‡ 0.6092	4 mg to 10 mg pre-chemo and every 6 to 12 hours**	$1.22 to $6.09 (daily)

cap=capsule; chemo=chemotherapy; IV=intravenously; ODT=orally disintegrating tablet; O/L=oral liquid; tab= tablet.
Source: Ontario Drug Benefit / Comparative Drug Index (effective from September 4, 2007)
*Manufacturer's (Merck Frosst Canada Ltd.) submission binder
†Guidelines for the Management of Nausea and Vomiting in Cancer Patients, Cancer Care Nova Scotia 2004
‡Saskatchewan Formulary (effective from July 1, 2007)
**Therapeutic Choices (chapter 109)[30]

Table 5: Antiemetic Regimens for HEC				
Treatment Regimen	**Day of Regimen**	**Drugs**	**Cost ($)**	**Total Cost per Regimen**
Aprepitant Regimen	1	Aprepitant 125 mg daily Ondansetron 32 mg IV daily Dexamethasone 12 mg	30* 106* 2	**$201**
	2	Aprepitant 80 mg daily Dexamethasone 8 mg daily	30* 1	
	3	Aprepitant 80 mg daily Dexamethasone 8 mg daily	30* 1	
	4	Dexamethasone 8 mg daily	1	
Usual Care – Study 801*	1	Ondansetron 32 mg IV daily Dexamethasone 20 mg daily	106* 3	**$169**
	2	Ondansetron 8 mg twice daily Dexamethasone 8 mg twice daily	18 2	
	3	Ondansetron 8 mg twice daily Dexamethasone 8 mg twice daily	18 2	
	4	Ondansetron 8 mg twice daily Dexamethasone 8 mg twice daily	18 2	
Usual Care – Study 052/054	1	Ondansetron 32 mg IV daily Dexamethasone 20 mg daily	106* 3	**$115**
	2	Dexamethasone 8 mg twice daily	2	
	3	Dexamethasone 8 mg twice daily	2	
	4	Dexamethasone 8 mg twice daily	2	

IV=intravenously.

Source: Ontario Drug Benefit / Comparative Drug Index (effective from September 4, 2007)
* Manufacturer's (Merck Frosst Canada Ltd.) submission binder

Table 6: Antiemetic Regimens for MEC—as detailed in Study 071				
Treatment Regimen	**Day of Regimen**	**Drugs**	**Cost ($)**	**Total Cost per Regimen**
Aprepitant Regimen	1	Aprepitant 125 mg daily Ondansetron 8 mg twice daily Dexamethasone 12 mg daily	30* 18 2	**$110**
	2	Aprepitant 80 mg daily	30*	
	3	Aprepitant 80 mg daily	30*	
Usual Care	1	Ondansetron 8 mg twice daily Dexamethasone 20 mg daily	18 3	**$57**
	2	Ondansetron 8 mg twice daily	18	
	3	Ondansetron 8 mg twice daily	18	

Source: Ontario Drug Benefit / Comparative Drug Index (effective from September 4, 2007)
* Manufacturer's (Merck Frosst Canada Ltd.) submission binder

Results (as submitted by the manufacturer)

HEC

- $146 per additional responder (those experiencing no emesis and requiring no rescue medication)
- $21,149 per quality-adjusted life year (QALY) gained

MEC

- $575 per additional responder
- $126,506 per QALY gained

Pharmacoeconomic Analysis Discussion Points

- *Comparator regimens*. In both analyses, HEC and MEC, the comparator regimens include ondansetron in delayed phase CINV, which differs from the regimen used in studies 052 and 054. There is some evidence that the use of ondansetron in the delayed phase may not improve clinical outcomes; however, as argued by the manufacturer and supported by clinical experts, it is prescribed for the delayed phase by some physicians. This may be due to the lack of treatment options. The authors have attempted to consider the differing treatment practices with ondansetron by varying the number of days 5-HT_3 antagonists would be administered in their sensitivity analyses without varying the efficacy parameters. Where ondansetron is used only in the acute phase (day one), the cost per QALY increases to $101,340 for HEC and $220,000 for MEC. These estimates are more reflective of the results from published economic evaluations for aprepitant.
- *Derivation of transition probabilities for nausea*. The definition of complete responder (no emesis and no rescue therapy) may be independent of the level of nausea depending on the definition used. The inclusion of nausea in the model is based on unpublished data from the clinical trials. Consequently, the CDR was unable to confirm these estimates.
- *Utility scores*. The utility values were obtained from 25 Canadian oncology nurses and pharmacists using a time trade-off interview.[29] The study was conducted to gain insight into the patients on antiemetic therapy who are receiving HEC. The transferability of utility values to a population receiving MEC is unclear and has not been addressed by the authors. Also, the exercise captured the utility values associated with varying degree for emesis but does not capture any aspects of nausea. How the lack of benefit in symptoms of nausea, as seen in the clinical trials, affects QoL has not been fully explored in the analyses.
- *Multiple days of chemotherapy*. Limited clinical information is available on multi-day chemotherapy regimens – one clinical trial of 36 patients.[31] The results provided by the manufacturer apply to the first chemotherapy cycle; the applicability of the results to subsequent chemotherapy cycles is unknown. Also, how an aprepitant regimen will be used for multi-day chemotherapy has not been addressed in the economic submission.

Summary of the Clinical and Pharmacoeconomic Reviews

HEC

- Regimens using aprepitant as an adjunctive agent were more effective than control regimens of ondansetron (a 5-HT_3 antagonist) and dexamethasone in reducing chemotherapy-induced vomiting.

- Regimens using aprepitant as an adjunctive agent did not consistently reduce nausea associated with chemotherapy.
- Improvements in QoL were also observed with aprepitant.
- Use of rescue therapy was reduced in two of three studies reviewed.
- Aprepitant costs $146 per additional complete responder (those experiencing no emesis and requiring no rescue medication) compared to a regimen without aprepitant.
- The incremental cost per QALY gained for aprepitant is $21,000 compared to a regimen without aprepitant.
- The cost per QALY increases to $101,300 if the 5-$HT_3$ antagonist is assumed to be used only on day one of chemotherapy.

MEC

- Reductions in vomiting with regimens using aprepitant were reported.
- No reductions in the use of rescue therapy with aprepitant were found.
- QoL measures were improved with aprepitant.
- The number of patients experiencing nausea was not reduced.
- Aprepitant costs $575 per additional complete responder (those experiencing no emesis and requiring no rescue medication) compared to a regimen without aprepitant.
- The incremental cost per QALY gained for aprepitant is $126,500 compared to a regimen without aprepitant.
- The cost per QALY increases to $220,000 if the 5-$HT_3$ antagonist is assumed to be used only on day one of chemotherapy.

In general:

- Interpretation of the efficacy data in the included trials is confounded by the effect of the pharmacokinetic interaction between aprepitant and dexamethasone.
- There were no significant differences in harms data between groups of patients receiving adjunctive aprepitant or a standard antiemetic treatment regimen.

CEDAC Final Recommendation — Issued February 20, 2008

Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, CEDAC recommended that aprepitant, when used in combination with a 5-HT_3 antagonist and dexamethasone, be listed for the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy (e.g., cisplatin >70 mg/m^2) in patients who have experienced emesis, despite treatment with a combination of a 5-HT_3 antagonist and dexamethasone, in a previous cycle of highly emetogenic therapy.

APPENDIX I: Methodology for the Full CDR Clinical Review

Methods

Reviewer Information

- The Systematic Review of the Clinical Trials section was prepared by two CDR clinical reviewers in consultation with an external clinical expert who specializes in oncology and internal medicine.
- The Supplemental Issues section was prepared by two CDR clinical reviewers.
- Background Information on the Condition (Appendix I) was prepared by a clinical reviewer, in collaboration with an external clinical expert who specializes in oncology and internal medicine.

Systematic Review Methods

Review Protocol

- The review protocol was developed by the two clinical reviewers and the external clinical expert in consultation with the pharmacoeconomic reviewers. Members of the Canadian Expert Drug Advisory Committee (CEDAC) also provided input and comments.

Literature Search Methods

- The literature search was performed by an internal CDR information specialist using a peer-reviewed search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE and Medline through OVID, and The Cochrane Library (2007, Issue 3) through Wiley InterScience.
- Retrieval was limited to the human population, but was not limited by publication year or language. The initial search was completed on September 18, 2007. Regular alerts were established to update the search until CEDAC's January 23, 2008 meeting.
- Grey literature was obtained by searching the web sites of regulatory, health technology assessment and “near”-technology assessment agencies, and clinical trial registries. Google™ and other Internet search engines were used to search for a variety of web-based information including conference abstracts.
- The drug manufacturer was contacted for additional trial data.

Selection of Studies

- Each clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Selection Criteria

- Studies were chosen for inclusion in the review based on the criteria listed in Table 1, located in the body of this report.

Quality Assessment

- Study bias was critically assessed independently by the two CDR clinical reviewers.

Data Analysis Methods

- CDR reviewers performed statistical analyses using SAS statistical software (release 9.1.3, SAS Institute, Cary, NC).

Methods for Supplemental Issues

- In addition to the systematic review, a number of supplemental issues were considered and reported within a four-page supplemental issue section.

APPENDIX II: Quality of Life (QoL) Outcome Measure: Functional Living Index-Emesis (FLIE)

The FLIE scale is used as an outcome measure in cancer-related antiemetic studies and was designed as an easy to use, patient-administered scale to assess the impact of CINV on patients' daily function.[32-34] First reported in 1992, the FLIE is an 18-item emesis- and nausea-specific QoL questionnaire that was derived from the multi-dimensional Functional Living Index-Cancer.[32] For each of the two domains of emesis and nausea, the FLIE has nine identical items; the first item quantifies the problem and the remaining eight items assess impact on daily life (e.g., ability to enjoy meals, ability to perform daily functions, and willingness to spend time with friends and family.)[33] Patients complete the FLIE periodic recall questionnaires that may use information from daily diaries recorded during treatment.

Each item is answered along a continuous gradient that is divided into six sections and anchored by the numbers 1 and 7 where 1 corresponds to "a great deal" (of impact on daily life) and 7 corresponds to "none/not at all." Higher scores are more favourable and reflect less negative impact. The total score is a sum of the scores for all 18 items and can range from 18 (where all items receive the unfavourable score of 1) to 126 (where all items receive the favourable score of 7).[34] The FLIE can also be interpreted through separate scores for emesis and nausea, and individual scores for each of the 18 items.[33,35] An endpoint that is commonly employed for between-group differences is termed "no impact on daily life" where the average FLIE item scores are >6.[33]

The FLIE was originally developed to assess the impact of CINV during the first three days of chemotherapy. It was expanded to assess the acute and delayed phases of CINV during a five-day period. The FLIE developers validated the instrument through psychometric assessment;[32] subsequent researchers have also considered it to be a valid scale.[35-37]

REFERENCES

1. Hesketh PJ. Pathophysiology and prediction of chemotherapy-induced emesis. In: *UpToDate* [database online]. Version 15.2. Waltham (MA): UpToDate; 2007.
2. Kris MG, Hesketh PJ, Herrstedt J, Rittenberg C, Einhorn LH, Grunberg S, et al. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy. *Support Care Cancer* 2005;13(2):85-96.
3. Schwartzberg LS. Chemotherapy-induced nausea and vomiting: clinician and patient perspectives. *J Support Oncol* 2007;5(2 Suppl 1):5-12. Available: http://www.supportiveoncology.net/journal/articles/0502s105.pdf (accessed 2008 Mar 7).
4. Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. *J Clin Oncol* 2005;23(6):1289-94. Available: http://jco.ascopubs.org/cgi/reprint/23/6/1289 (accessed 2007 Oct 2).
5. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol* 1999;17(9):2971-94. Available: http://jco.ascopubs.org/cgi/reprint/17/9/2971 (accessed 2007 Sep 25).
6. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;21(22):4112-9.
7. de Wit R, Herrstedt J, Rapoport B, Carides AD, Carides G, Elmer M, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol* 2003;21(22):4105-11.
8. Schmoll HJ, Aapro MS, Poli-Bigelli S, Kim HK, Park K, Jordan K, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. *Ann Oncol* 2006;17(6):1000-6.
9. de Wit R, Herrstedt J, Rapoport B, Carides AD, Guoguang-Ma J, Elmer M, et al. The oral NK_1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur J Cancer* 2004;40(3):403-10.
10. Gralla RJ, de Wit R, Herrstedt J, Carides AD, Ianus J, Guoguang-Ma J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a $5HT_3$ antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two Phase III randomized clinical trials. *Cancer* 2005;104(4):864-8.
11. Aapro MS, Schmoll HJ, Poli-Bigelli S, Jordan K, von Pawel J, Giezek H, et al. Comparison of aprepitant combination regimen with 4-day ondansetron + 4-day dexamethasone for prevention of acute and delayed nausea/vomiting after cisplatin chemotherapy [abstract]. *J Clin Oncol* 2005;23(16 Suppl):8007. Available: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/8007 (accessed 2008 Mar 5).
12. Warr DG, Grunberg SM, Gralla RJ, Hesketh PJ, Roila F, Wit R, et al. The oral NK_1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. *Eur J Cancer* 2005;41(9):1278-85.

13. Moss HB, Herrstedt J, Hesketh P, Warr D, Gabriel M, Rodgers A, et al. Randomized, double-blind trial comparing the effect of an aprepitant regimen versus a standard antiemetic regimen during four cycles of moderately emetogenic chemotherapy [abstract]. *Breast Cancer Res Treat* 2004;88 Suppl 1:S229.

14. Hesketh PJ, Grunberg SM, Herrstedt J, de Wit R, Gralla RJ, Carides AD, et al. Combined data from two phase III trials of the NK1 antagonist aprepitant plus a 5HT 3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. *Support Care Cancer* 2006;14(4):354-60.

15. Gralla R, Hesketh P, Grunberg S, Warr D, Roila F, Chawla S, et al. The oral NK1 antagonist aprepitant for the prevention of chemotherapy induced nausea and vomiting: Pooled data from 2 randomized, double-blind, placebo controlled trials [abstract]. *EJC Suppl* 2003;1(5):S207.

16. Gralla RJ, Carides AD, Ianus J, Elmer M, Evans JK, Horgan KJ. The oral neurokinin-1 antagonist aprepitant added to standard antiemetics provided equal efficacy in female and male patients receiving highly emetogenic chemotherapy: Combined data from 2 phase III clinical trials [abstract]. *Breast Cancer Res Treat* 2003;82 Suppl 1:S153.

17. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, 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(12):2822-30.

18. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie MG, Eldridge K, Hipple A, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97(12):3090-8.

19. Horgan K, Grunberg S, Hesketh P, Guoguang-Ma J, Ianus J, Evans J, et al. Analysis of pooled data from two Phase III studies of the NK-1 antagonist aprepitant to assess relationships between the incidence and control of cisplatin-induced acute vomiting and delayed vomiting [abstract]. *EJC Suppl* 2003;1(5):S284-S285.

20. Herrstedt J, Muss HB, Warr DG, Hesketh PJ, Eisenberg PD, Raftopoulos H, 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(7):1548-55.

21. Gralla RJ, Warr DG, Carides AD, Evans JK, Horgan KJ. Effect of aprepitant on antiemetic protection in patients receiving moderately emetogenic chemotherapy plus high-dose cisplatin: Analysis of combined data from 2 phase III randomized clinical trials [abstract]. 40th Annual Meeting of the American Society of Clinical Oncology; 2004 Jun 5; New Orleans (LA). Abstract no 8137.

22. Warr DG, Eisenberg P, Hesketh PJ, Gralla RJ, Muss H, Raftopolous H, et al. Effect of aprepitant for the prevention of nausea and vomiting after one cycle of moderately emetogenic chemotherapy: A randomized double-blind trial in 866 patients [abstract]. *J Clin Oncol* 2004;22(14 Suppl):8007. Available: http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/8007 (accessed 2008 Mar 5).

23. *Health Canada reviewer's report: Emend (aprepitant)* [**CONFIDENTIAL** internal report]. Ottawa: Therapeutic Products Directorate, Health Canada; 2007.

24. *CDR submission binder. Emend™ (aprepitant, MSD) (aprepitant 80mg & 125mg tablets)* [**CONFIDENTIAL** internal manufacturer's report]. Kirkland (QC): Merck Frosst Canada; 2007 Aug.

25. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: *Emend (aprepitant). Company: Merck. Application no:(NDA) 021549. Approval date: 03/26/2003* [FDA approval package]. Rockville (MD): The Center; 2003. Available: http://www.fda.gov/cder/foi/nda/2003/21-549_Emend.htm (accessed 2008 Mar 7).

26. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: *Emend (aprepitant). Company: Merck. Application no:(NDA) 021549. Approval date: 03/26/2003* [FDA approval package]. Rockville (MD): The Center; 2003. Available: http://www.fda.gov/cder/foi/nda/2003/21-549_Emend.htm (accessed 2008 Mar 7).

27. Gastrointestinal Drugs Advisory Committee, U.S. Food and Drug Administration. *Background information regarding EMEND™ (Aprepitant) capsules, Merck Research Lab*. Rockville (MD): U.S. Food and Drug Administration; 2003 Mar 6. Available: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3928b1.htm (accessed 2007 Oct 16).

28. McCrea JB, Majumdar AK, Goldberg MR, Iwamoto M, Gargano C, Panebianco DL, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003;74(1):17-24.

29. Dranitsaris G, Leung P. Using decision modeling to determine pricing of new pharmaceuticals: the case of neurokinin-1 receptor antagonist antiemetics for cancer chemotherapy. *Int J Technol Assess Health Care* 2004;20(3):289-95.

30. Gray J, editor. *Therapeutic choices*. 4th ed. Ottawa: Canadian Pharmacists Association; 2003.

31. Joshi AJ, Singh H, Chawla S. Prevention of chemotherapy-induced delayed nausea and vomiting with aprepitant in patients recieving highly emetogenic-five day cisplatin regimens [abstract]. *J Clin Oncol* 2007;25(18 Suppl):14125. Available: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/14125 (accessed 2008 Mar 5).

32. Lindley CM, Hirsch JD, O'Neill CV, Transau MC, Gilbert CS, Osterhaus JT. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res* 1992;1(5):331-40.

33. Martin AR, Carides AD, Pearson JD, Horgan K, Elmer M, Schmidt C, et al. Functional relevance of antiemetic control. Experience using the FLIE questionnaire in a randomised study of the NK-1 antagonist aprepitant. *Eur J Cancer* 2003;39(10):1395-401.

34. Frank-Stromborg M, Olsen S. *Instruments for clinical health-care research*. 3rd ed. Sudbury (MA): Jones and Bartlett; 2004.

35. Decker GM, DeMeyer ES, Kisko DL. Measuring the maintenance of daily life activities using the functional living index-emesis (FLIE) in patients receiving moderately emetogenic chemotherapy. *J Support Oncol* 2006;4(1):35-41, 52. Available: http://www.supportiveoncology.net/journal/articles/0401035.pdf (accessed 2007 Oct 25).

36. Pearson J, Blumentals W, Martin A, Carides A, Horgan K, Wittreich J, et al. Validation of Functional Living Index-Emesis (FLIE) quality-of-life questionnaire for acute and delayed chemotherapy-induced emesis. *Proc Am Soc Clin Oncol* 2000;19:Abstract 2384. Available: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=2&index=y&abstractID=202408 (accessed 2007 Oct 25).

37. Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. *Support Care Cancer* 2003;11(8):522-7.