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Economic evaluation of prophylactic antiemetic regimens for prevention of chemotherapy -induced nausea and vomiting (CINV)

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ECONOMIC EVALUATION OF PROPHYLACTIC ANTIEMETIC REGIMENS FOR PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

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ABSTRACT

Economic Evaluation of Prophylactic Antiemetic Regimens for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV)

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New antiemetic agents, aprepitant and palonosetron have been approved for prevention of chemotherapy-induced nausea and vomiting (CINV). The objectives of the two phases of the study were: 1) to conduct cost-effectiveness analysis of antiemetic regimens for prevention of CINV in patients receiving highly emetogenic chemotherapy (HEC) and in patients receiving moderately emetogenic chemotherapy (MEC) using decision models, and 2) to determine the monetary value of improved emesis control and conduct cost-benefit analysis of the new antiemetic regimens. Regimen A, one of the four antiemetic strategies included in the HEC decision model was a combination of aprepitant and the standard regimen of ondansetron+dexamethasone. The other three regimens had standard regimen in the acute phase but differed in the delayed phase regimens: regimen B - dexamethasone only, regimen C - dexamethasone+metoclopramide and regimen D - dexamethasone+ondansetron. The four antiemetic strategies for prevention of CINV due to MEC were: regimen 1) IV palonosetron, 2) IV ondansetron, 3) ondansetron+dexamethasone in acute phase, only dexamethasone in delayed phase, 4) ondansetron+dexamethasone in acute and delayed phase. The outcome measure was the incremental cost-effectiveness ratios (ICER) measured as cost/patient with complete control of emesis. For the HEC model, the ICER of regimen A compared to C was $3,363.18 and $2,881.61 per patient with complete control of emesis, from payer and societal perspectives respectively. One-way and probabilistic sensitivity analyses indicated that the conclusions were relatively stable to variations in multiple parameters. For MEC model, regimen 1 was found to be most cost-effective with ICER of $3,582.48 and $3,549.02, from payer and societal perspectives respectively. Overall, the ICER results showed that the regimen A and regimen 1 could be considered cost-effective therapies for prevention of CINV. In phase II, a contingent valuation survey was developed and administered to 120 cancer patients who were either receiving or had received chemotherapy. The results showed that respondents were willing-to-pay on average $83.50 for a single dose of palonosetron and $89.90 for a three-day regimen of aprepitant. Phase II qualitative results also emphasized that cancer patients receiving chemotherapy placed a high importance on receiving even a modest improvement in the control of CINV.

DEDICATION

This research is dedicated to

My Parents

RAMESH AND SARLA MODY

&

My Friend and Husband

RAHUL

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CHAPTER ONE

INTRODUCTION

1.1: Epidemiology of Chemotherapy-Induced Nausea and Vomiting (CINV)

Chemotherapy, one of the mainstays in the treatment of cancer has two main goals: 1) to control the progression of tumors and increase survival and 2) to improve health-related quality of life (HRQOL). In 2001, approximately 1.4 million cancer patients in the United States (US) received chemotherapy. It is also estimated that almost 600,000 of the approximately 1.4 million newly diagnosed cancer patients per year are candidates for cancer chemotherapy (Plosker & Benfield, 1996). However, chemotherapy drugs are associated with a number of adverse effects such as nausea, vomiting, anemia, neutropenia, alopecia, constipation, diarrhea and stomatitis (DeVita, Hellman, & Rosenberg, 2001).

Chemotherapy-induced nausea and vomiting (CINV) are perceived among the most distressing side effects of chemotherapy by patients with cancer (Boer-Dennert et al., 1997; Griffin et al., 1996). A study conducted in 1983, assessing patients' perceptions of side effects of cancer chemotherapy, before the introduction of 5-HT_3 receptor antagonists (5-HT_3 RAs), showed that nausea and vomiting were ranked as the most distressing side effects (Coates, et al., 1983). More recent studies showed that CINV is still ranked among the top five distressing side effects of chemotherapy, despite the development of efficacious antiemetic agents (Boer-Dennert et al., 1997; Griffin et al., 1996). However, a study conducted (Carelle et al., 2002) in French patients showed that patients' perceptions of the side effects of cancer chemotherapy had changed, with fatigue and psychosocial concerns predominating compared to emesis and nausea.

The actual incidence and severity of nausea and vomiting is difficult to determine due to: type of chemotherapy given, dose, schedule, individual patient characteristics, health condition of patients who receive the chemotherapy drugs, underassessment by clinicians and underreporting by patients (Doherty, 1999; Osoba, et al., 1997a). Irrespective of various factors, approximately 60% to 80% of all cancer patients receiving chemotherapy experience some degree of nausea and vomiting (King, 1997). Based on the time of its occurrence, CINV can be classified into acute, delayed and anticipatory CINV (Refer Chapter 2 for definitions). Among patients treated with

highly emetogenic (HE) chemotherapy (such as cisplatin) and not receiving any prophylaxis for CINV, the incidence of acute and delayed emesis is more than 90% and between 60-90%, respectively. Similarly, in patients receiving moderately emetogenic (ME) chemotherapy agents (such as carboplatin, cyclophosphamide or doxorubicin), the incidence of acute and delayed emesis is between 30-90% and 20-33% respectively (Gralla, 1997; Gralla et al., 1999; Hesketh, 1999).

1.2: Impact of CINV on Clinical, Humanistic and Economic Outcomes

Impact on clinical outcomes

Uncontrolled and suboptimally controlled CINV may lead to physiological consequences such as fluid and electrolyte disturbances, dehydration, esophageal tears, weight loss, aspiration pneumonia and liver function abnormalities (Bender et al., 2002). The goal for chemotherapy patients is to maintain adequate nutritional intake to prevent weight loss and to maintain protein stores and muscle mass. However, prolonged or delayed nausea and vomiting may lead to inadequate nutritional intake leading to weight loss and muscle wasting (Brown et al., 2001). Poor emesis control can also lead to anticipatory nausea and vomiting in 10-30% of the patients (Boakes, Tarrier, Barnes, & Tattersall, 1993). It can also lead to psychological effects that may lead to depression and anxiety. Though hospitalizations for complications of emesis are rare (Feldman & Dixon, 2000), failure to control treatment-related nausea and vomiting can lead to 20-50% of patients delaying or refusing possible lifesaving chemotherapy (Herrstedt, 2002; Schnell, 2003).

Impact on humanistic outcomes

Health-related quality of life (HRQOL) is a subjective, multidimensional perspective of well-being that is influenced by disease and treatment (Grant, 1997). It is an important outcome measure of patient response to cancer and cancer treatment. CINV affects the physical, psychological, spiritual and social well-being of the patient (Grant, 1997). A review article of various observational studies showed that, after adjusting for HRQOL before chemotherapy, CINV was associated with a decrease in HRQOL of patients with emesis compared to patients without emesis (Ballatori & Roila, 2003).

Osoba et al.(Osoba et al., 1997b) studied the effect of post-chemotherapy nausea and vomiting on HRQOL among 802 cancer patients receiving HE and ME chemotherapy. The

patients completed the European Organization for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire before and 7 days after the first chemotherapy dose, and on the first day of the second cycle of chemotherapy. It was found that the group with nausea and vomiting showed significantly worse physical, cognitive and social functioning as compared to the group that did not experience nausea or vomiting. The group with nausea and vomiting also had worse scores on global quality of life, fatigue, anorexia, insomnia and dyspnea. Patients with only nausea tended to have less worsening in functioning and symptoms than those having both nausea and vomiting. Increased severity of vomiting (> 2 episodes) was associated with worsening of global quality of life and anorexia compared with one to two episodes of vomiting.

Lindley et al. (Lindley et al., 1992) conducted a study among 122 patients with various cancers, receiving different chemotherapy and antiemetic regimens to evaluate the impact of CINV on quality of life (QOL). The Functional Living Index – Emesis (FLIE), a validated instrument was administered at baseline and three days after chemotherapy to study the impact of CINV on physical activities, social and emotional function and ability to enjoy meals. There was a significant decrease in the mean QOL score of patients who experienced emesis compared to the non-emesis patient group. CINV also has an impact on daily life such as maintaining hobbies, preparing a meal or carrying out minor tasks around the house etc. A cross-sectional multinational study conducted to assess the impact of CINV on daily life showed that 77% of patients who suffered from nausea and 53% of those suffering from vomiting reported a negative impact on their daily life (Glaus et al., 2004).

Though studies have shown that CINV has a significant impact on patients' HRQOL, it is difficult to quantify the impact of uncontrolled CINV on intangible effects such as HRQOL, patient distress and suffering. These intangible effects can be valued either by using monetary values or by using economic and psychometric scaling techniques.

Impact on economic outcomes

In addition to its clinical impact, uncontrolled nausea and vomiting also have significant economic burden. Uncontrolled CINV and subsequent medical complications can lead to increase in the direct, indirect and intangible costs associated with CINV. Direct costs associated with CINV include cost of prophylactic and rescue medications, health care personnel costs, extended hospitalizations and material costs, whereas indirect costs include lost or reduced patient/caregiver productivity and lost income (Miller & Kearney, 2004; Pendergrass, 1998).

The intangible costs associated with uncontrolled CINV include decreased QOL, patient distress and patient suffering.

The information on costs of CINV is limited due to very few published studies. Before the introduction of costlier and more effective 5-HT_3RAs to prevent CINV, the direct and indirect costs associated with CINV in Canadian cancer centers were approximately US $127 per patient (O'Brien et al., 1993). The direct costs associated with CINV included cost of prophylactic and rescue medications, nurse time, physician time, hospital admissions, and material costs. Indirect costs which accounted for two-thirds of the total costs included the out-of-pocket expenses for the purchase of nonprescription medicines, travel costs, and patient or caregiver time away from work. The study also reported a total loss of 198 hours of paid employment and 409 hours of unpaid employment, among 72 patients who experienced emesis. An additional loss of 186 hours was found among caregivers.

A more recent, prospective, cross-sectional, cost-of-illness study conducted in German cancer centers showed that the most frequently used resources due to delayed emesis were rescue medications, outpatient hospital and physician office visits (Ihbe-Heffinger et al., 2004). In 2002, the mean direct and indirect costs per treatment cycle with CINV per patient was €77.30±146.59 (US $93.37±177.06). In this study, one patient required hospitalization and three patients lost workdays due to delayed CINV. However, this study did not consider cost associated with lost personal time from daily activities and lost unpaid work due to CINV. In another study, Roila and colleagues (2000) showed that of patients who experienced CINV, 23% were unable to go to work, 22% reported they were unable to prepare meals, and 12% were unable to take prescribed medications. The impact of CINV on work productivity and daily life activities were not quantified in this study. Thus, uncontrolled CINV poses a significant economic burden on the patient in the form of direct medical and indirect costs. The intangible costs associated with uncontrolled or suboptimally controlled CINV have not been assessed satisfactorily. Though there are only a few cost-of-burden studies in the area of CINV, it is difficult to compare the results due to variation in methodology employed, study setting, study country and availability of various antiemetic agents.

1.3: Prevention Strategies for CINV

The most important point about managing CINV is that preventing CINV is more effective than treating it (Markman, 2002). Antiemetic agents administered before chemotherapy are effective in reducing the incidence of acute emesis, but it is difficult to completely control CINV once it has begun. Thus, prophylaxis with appropriate antiemetic agents is very critical in preventing acute, delayed and anticipatory emesis during the first and subsequent cycles of chemotherapy. One of the goals of antiemetic therapy is to achieve complete control in all settings, beginning with the initial cycle of chemotherapy, thus improving patient compliance, quality of life, and preventing development of anticipatory and refractory nausea and vomiting during subsequent cycles of chemotherapy.

Various classes of drugs such as phenothiazines, butryophenones, substituted benzamides, cannabinoids, steroids and 5-HT_3 receptor antagonists (5-HT_3 RA) are available to control the incidence of CINV (Gralla, 1997). Due to the side effect profile of older antiemetic agents such as phenothiazines, butyrophenones and substituted benzamides, these are primarily used as rescue medications for breakthrough emesis.

5-HT_3 Receptor Antagonists (5-HT_3 RAs)

Due to its high efficacy and favorable toxicity profile compared to other antiemetic agents, 5-HT_3 RAs are currently the first-line agents and the gold standard for prevention of CINV in patients receiving HE or ME chemotherapy (Gralla et al., 1999; Schnell, 2003). These agents exert their antiemetic activity by antagonism of 5-HT_3 receptors. As monotherapy, the 5-HT_3 RAs provide complete acute antiemetic protection, i.e. no nausea, no vomiting and no use of rescue medications, in 40-60% of patients receiving cisplatin based chemotherapy and 60-80% of patients receiving ME chemotherapy (Schnell, 2003). In patients receiving high-dose cisplatin-based chemotherapy regimens, 5-HT_3 RAs provides complete antiemetic protection in the acute phase in 25-60% of patients (Audhuy et al., 1996; Beck et al., 1992; P. Hesketh et al., 1996; Marty et al., 1995; Navari et al., 1995). Three 5-HT_3 RAs are currently available in the US for prevention of emesis: dolasetron (Anzemet), granisetron (Kytril) and ondansetron (Zofran). Several randomized, controlled studies have shown that ondansetron, granisetron and dolasetron have equivalent complete control rates, defined as complete absence of nausea or vomiting, among patients receiving HE or ME chemotherapy (Berger & Clark-Snow, 2001; Gralla et al., 1998; Hesketh, 2000).

Though the existing antiemetic regimens provide reasonably good protection against acute emesis, they do not provide adequate protection against delayed emesis, with approximately 50% of patients experiencing delayed emesis (Olver et al., 1996). In addition, 5-HT_3 RAs have not demonstrated sustainable efficacy in controlling CINV over repeated cycles of chemotherapy (de Wit et al., 1996; de Wit et al., 1998). Due to the shortcomings of the existing antiemetic agents, newer agents with better efficacy were needed and have been recently introduced in the market. Two such antiemetic agents are aprepitant (Emend®) and palonosteron (Aloxi®).

New Antiemetic Agents

Aprepitant (Emend®)

Aprepitant is the first oral selective nonpeptide NK-1 receptor antagonist indicated for use in combination with a 5-HT_3RA and a corticosteroid for prevention of acute and delayed emesis due to HE chemotherapy regimens (Emend® Monograph). Aprepitant, in a dose of 125 mg, is recommended as a part of combination antiemetic regimen with a corticosteroid and a 5-HT_3 RA prior to chemotherapy (day one) and a dose of 80 mg on day two and three. The results of two large phase III clinical trials showed that the aprepitant based regimen had superior antiemetic efficacy as compared to the standard regimen in patients receiving high-dose cisplatin ($\geq$70mg/m^2) (Hesketh et al., 2003; Poli-Bigelli et al., 2003).

Studies also showed that the antiemetic efficacy of aprepitant is maintained over multiple cycles of chemotherapy (de Wit et al., 2003; de Wit et al., 2004). But aprepitant has not been shown to mitigate ongoing emetic symptoms and has not been tested for continuous use for duration greater than five days in patients receiving emetogenic chemotherapy. Although addition of aprepitant improved overall antiemetic protection, the 2005 average wholesale price (AWP) of $309.00 for a three-day regimen (Red Book, 2005) makes it expensive compared to the other antiemetic agents used for prevention of acute and delayed emesis following administration of HE chemotherapy.

Palonosetron (Aloxi®)

Palonosetron, a 5-HT_3 RA, is an injectable antiemetic agent with a higher binding affinity to the 5-HT_3 receptors, a higher potency and a longer half-life compared to the older 5-HT_3 RAs. It is indicated for prevention of acute emesis due to HE regimens and prevention of acute and

delayed emesis due to ME regimens (Aloxi® Monograph). In patients receiving HE chemotherapy, including cisplatin, a single 0.25 mg intravenous (IV) dose of palonosetron was at least as effective as a 32 mg IV dose of ondansetron for acute and delayed emesis. In patients receiving ME chemotherapy, a 0.25 mg IV dose of palonosetron is at least as effective as a 100 mg IV dose of dolasetron, but the former regimen provides superior antiemetic protection in the delayed phase (Eisenberg et al., 2003; Gralla et al., 2003). Compared to the older 5-HT_3 RAs, palonosetron provides the convenience of a single dose schedule for prevention of emesis. More clinical trials of combination antiemetic regimens with palonosetron need to be carried out to establish whether it is more efficacious than the combination of a corticosteroid with either metoclopramide or a 5-HT_3 RA for protection of delayed emesis due to HE chemotherapy. With the 2005 AWP of a 0.25mg 5 ml single dose vial at $340.20 (Red Book, 2005), palonosetron is expensive as compared to the older 5-HT_3 RAs.

1.4: Combination antiemetic regimens and Recommendations for Antiemetic Use

Combination of two or more antiemetic agents provides better efficacy than a single antiemetic agent in prevention of CINV following the administration of HE and ME chemotherapy. Several professional organizations such as the Multinational Association of Supportive Cancer Care (MASCC), the American Society of Clinical Oncology (ASCO), the American Society of Health-System Pharmacists (ASHP), the National Comprehensive Cancer Network (NCCN), and the Canadian Medical Association have published guidelines and evidence-based recommendations for the use of antiemetics in management of CINV (ASHP, 1999; ESMO, 2001; Gralla et al., 1999; MASCC, 1998; NCCN, 1997).

The 1999 ASCO and ASHP guidelines recommended a combination of dexamethasone and a 5-HT_3 RA (standard regimen) for prevention of acute emesis in patients receiving HE chemotherapy (ASHP, 1999; Gralla et al., 1999). A combination regimen of dexamethasone with either metoclopramide or a 5-HT_3 RA was recommended for prevention of delayed CINV following HE chemotherapy. With the introduction of aprepitant, new guidelines have been proposed by the NCCN and the MASCC for management of CINV. In patients receiving HE chemotherapy, a three-drug combination of aprepitant, dexamethasone and a 5-HT_3 RA is recommended for control of acute emesis. A combination of aprepitant and a corticosteroid, such as dexamethasone is now recommended for delayed emesis following HE chemotherapy.

In patients receiving ME chemotherapy regimens, combination of a corticosteroid and a 5-HT_3 RA is recommended for prevention of acute emesis (ASHP, 1999; Gralla et al., 1999). Previous guidelines have recommended the use of either dexamethasone alone or combination of dexamethasone with a 5-HT_3 RA or metoclopramide for prevention of delayed emesis due to ME chemotherapy (ASHP, 1999; Gralla et al., 1999). The 2005 NCCN and 2004 MASCC guidelines recommend using palonosetron as the 5-HT_3 RA for prevention of acute emesis and either dexamethasone alone or a 5-HT_3 RA alone for prevention of delayed emesis. If aprepitant was included in the antiemetic regimen during the acute phase, a combination of aprepitant and dexamethasone is recommended for prevention of delayed emesis (MASCC, 2004; NCCN, 2005).

1.5: Utilization of Prophylactic Antiemetics in Clinical Practice

As discussed earlier, various guidelines for appropriate prevention and management of CINV have been published. Results from observational studies showed that guideline recommendations were not transferred completely into clinical practice (DURTO, 2003). Studies have shown that despite evidence from randomized clinical trials and publication of various guidelines and recommendations, there is underutilization of antiemetic drugs to prevent delayed emesis (Mertens et al., 2003; Roila, 2004; Roila, Donati, Tamberi, & Margutti, 2002).

A drug utilization study was undertaken to determine if the 1999 MASCC antiemetic guidelines for prevention of CINV were followed in clinical practice. The study was conducted among 87 Italian oncological centers in breast cancer patients undergoing chemotherapy with moderate to high emetic potential (DURTO, 2003). The study results showed that all chemotherapy patients received prophylactic antiemetics for acute emesis whereas only about 60% received prophylactic antiemetics for the delayed phase. Fifty six percent of patients received a combination of 5-HT_3RA and corticosteroid, the MASCC-recommended prophylaxis for acute emesis. The MASCC-recommended prophylaxis for delayed phase, a 5-HT_3RA, a corticosteroid or their combination was prescribed to 46% of patients. However, only 19.2% of patients received the ASCO and ESMO recommended prophylaxis for delayed emesis, such as, a corticosteroid alone or combined with either 5-HT_3RA or metoclopramide (ESMO, 2001; Gralla et al., 1999). Thus, the study results show that there are discrepancies between the recommendations for utilization of antiemetic regimens and their actual utilization in daily clinical practice.

Fabi and colleagues conducted a prospective, observational, longitudinal study to determine the appropriate prevention of delayed emesis in clinical practice (Fabi et al., 2003). The study results indicated that the clinical practice did not conform to the MASCC-recommended guidelines for prevention of nausea and vomiting. There were reports of underutilization of prophylaxis for prevention of delayed emesis and overtreatment with 5-HT_3RA in patients receiving chemotherapy with low emetic potential (Fabi et al., 2003; IGAR, 1998b). This inappropriate use of costly agents such as 5-HT_3RAs leads to increased costs to the health care system without a proportionate increase in the health benefits to patients. The present study makes an attempt to compare the regimen commonly employed in clinical practice as one of the strategies in the decision model designed to assess the cost-effectiveness of the new regimen.

1.6: Economics of Prevention of CINV

The introduction of serotonin receptor antagonists in the early 1990's made a significant impact on the prophylaxis and management of CINV. Compared to the older antiemetic agents, regimens with 5-HT_3RAs have resulted in better emesis control in patients receiving HE and ME chemotherapy. However, at the same time, these agents were costly compared to the older antiemetic agents. Rising health care expenditures coupled with limited resources have led to an increased interest in conducting economic evaluations of healthcare interventions, a method in which both costs and benefits of interventions are evaluated to make resource allocation decisions. In addition to using effectiveness information, it has become necessary to incorporate the economic aspects to determine the appropriateness of using new healthcare interventions in an increasingly cost-conscious environment. An important question that needs to be addressed is whether there are increased clinical, economic and humanistic benefits that will offset the increased cost of preventing CINV. Cost effectiveness analysis (CEA) is a technique applied when a choice must be made between two or more competing alternatives for which the expected health gain can be measured as one outcome measure, such as complete control of emesis.

A recent review of economic evaluations of antiemetic agents showed that the majority of the studies were conducted after the introduction of 5-HT_3RAs (Lachaine & Crott, 2003). A large proportion of these studies have been carried out in patients receiving HE chemotherapy (Ballatori et al., 1994; Becker et al., 1996; Buxton & O'Brien, 1992; Cunningham et al., 1993;

Sands, Roberts, Marsh, & Gill, 1992; Stewart, Dahrouge, Coyle, & Evans, 1999; Tejedor, Idoate, Jimenez, Sierrasesumaga, & Giraldez, 1999; Zbrozek, Cantor, Cardenas, & Hill, 1994), with some conducted in patients receiving ME chemotherapy (Cox & Hirsch, 1993; Johnson & Bosanquet, 1995; Johnson, Nash, Carpenter, & Sistek, 1993; Kwong & Parasuraman, 1999). Also, most of these studies have only evaluated the costs and benefits of antiemetic therapy during the acute phase of CINV. The economics of using combination antiemetic regimens for the delayed phase have not been adequately studied. Most of the economic evaluations conducted in the past compared 5-HT_3RAs to traditional agents such as metoclopramide or one 5-HT_3RA against another. The results from these studies showed that the additional cost due to use of 5-HT_3RAs is offset by a favorable side effect profile, lower personnel and administration costs and improved efficacy. These studies are explained in detail in Chapter 2.

Recently, three studies evaluating the cost effectiveness of aprepitant given with the standard regimen have been presented at international symposiums and published in abstract format (Deuson, 2004; Ehlken et al., 2004; Moore, Tumeh, Wojtanowski, & Flowers, 2005). Ehlken and colleagues conducted a cost-effectiveness evaluation of the three-drug regimen of aprepitant, dexamethasone and 5-HT_3 RA during the acute phase and combination of aprepitant and dexamethasone for the delayed phase (Deuson, 2004; Ehlken et al., 2004; Moore et al., 2005). The comparator for the economic evaluation was the standard regimen for the acute phase and dexamethasone for the delayed phase. In addition to the alternative used in the above economic evaluation, a comprehensive economic evaluation of antiemetics for prevention of CINV following HE chemotherapy comparing the new MASCC recommended regimen, old ASCO regimens and clinical practice is needed.

To our knowledge, there is only one published pharmacoeconomic analysis of palonosetron in patients receiving ME chemotherapy. The study was conducted from the payer's perspective and concluded that palonsetron is a cost-effective treatment strategy compared to the older 5-HT_3RAs (Vanscoy, Rubenstein, Smith, Weber, & Rihn, 2004). Notable also, the study did not compare the new regimen to previous ASCO-recommended guidelines and clinical practice for prevention of CINV following ME chemotherapy.

1.7: Need for the Study

CINV is a significant problem among cancer patients especially those receiving HE and ME chemotherapy. With the advent of new cytotoxic agents and colony stimulating factors, both of which facilitate more aggressive, and therefore potentially more emetogenic drug therapy, effective management of CINV by health professionals is imperative. As discussed earlier, uncontrolled or suboptimally controlled emesis has a considerable impact on clinical, economic and QOL outcomes. Though hospitalization due to severe emesis is rare, cost of prophylactic and rescue antiemetic medications pose a significant economic burden for third-party payers, hospitals and patients. With the advent of managed care, it is estimated that more than 70% of chemotherapy is administered in the outpatient setting in freestanding cancer centers, community oncology offices, comprehensive cancer centers, and ambulatory infusion suites (*Average Wholesale Price*, 2003).

Antiemetic agents used for prevention of CINV also form a substantial portion of the pharmacy budgets of managed care organizations, hospitals and cancer centers. The growing US market for the 5-HT_3 RAs is approximately $1.4 billion and includes the more than $800 million market for CINV prevention and treatment. With the entry of new agents such as aprepitant and palonosetron, new antiemetic guidelines and recommendations have been proposed by organizations such as the MASCC and the NCCN. These new guidelines recommend combination regimens, which include the new antiemetic drugs in addition to the old standard regimen. Though the new antiemetic regimens are more effective in controlling emesis, they increase the financial burden on managed care, hospital formulary budgets and patients. Oncology practitioners now have a number of new antiemetic regimens for use in preventing acute and delayed CINV. Since supportive care, which includes prevention of emesis is not perceived to directly affect cure, they are often targets for cost containment policies (Rubenstein, 1995a, 1995b). While, these policies focus on the high immediate drug procurement costs, they fail to incorporate the economic impact of therapies over the full course of the treatment in their reimbursement decisions (Rubenstein, 1995a, 1995b). An economic evaluation of supportive care therapies that incorporates a comprehensive assessment of direct, indirect and intangible costs and benefits of treatment will help demonstrate the value of the product.

Though cisplatin is no longer a widely used chemotherapy agent, economic evaluation of regimens for prevention of CINV following cisplatin administration is necessary because

practically all patients receiving it experience emesis if prophylactic treatment is not given. On the other hand, though the incidence and severity of emesis is lower in patients receiving ME chemotherapy, it represents the largest group of cancer patients who experience nausea and vomiting. Earlier economic evaluations compared different 5-HT_3 RAs with one another (five studies), or compared 5-HT_3 RA containing regimens with regimens containing older antiemetic agents (15 studies) such as metoclopramide, diphenhydramine, dexamethasone, methylprednisolone, and prochlorperazine. In addition, almost half of the economic evaluations were limited to acute nausea and vomiting following administration of chemotherapy (Lachaine & Laurier, 2002). A majority of the economic evaluations have compared treatment regimens that are no longer relevant and do not reflect the actual clinical practice of CINV management. Thus, an economic evaluation comparing new antiemetic guidelines to guidelines recommended prior to the introduction of new antiemetic agents, and also to widely used regimens in clinical practice for prevention of both acute and delayed emesis is required.

Cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA) which combines information on the health benefits, health risks and costs of health care services, are approaches that can incorporate and complement evidence on effectiveness for informed policy decision making. CINV has a significant impact on the QOL but has no known impact on survival of cancer patients. Thus antiemetic regimens that control acute and delayed CINV may lead to a significant qualitative improvement in survival but no quantitative change at all. Since HRQOL is now recognized as a primary outcome for the evaluation of supportive care therapies (Uyl-de Groot, Wait, & Buijt, 2000), it is necessary to incorporate the impact of CINV and its treatment on intangible outcomes such as HRQOL, patient suffering and distress in the form of preferences or utilities. Due to this, traditional cost-effectiveness analysis using life years gained may not be the most appropriate outcome measure in antiemetic economic evaluations. Cost per completely controlled patient is important from the payer and hospital perspective but outcome measures such as quality-adjusted life years (QALYS) or willingness-to-pay (WTP) that incorporate the effect of disease and treatment on QOL are more appropriate for use in antiemetic economic evaluations from a societal and patient perspective.

Zbrozek et al. (1995) performed a cost utility analysis comparing ondansetron with metoclopramide using efficacy data from published clinical trials. To calculate the incremental cost per QALY, a relative difference of 0.00014 QALY between two antiemetic agents was

arbitrarily estimated. The incremental cost per QALY in patients receiving high-dose cisplatin was US$407,667 and in patients receiving moderate-dose cisplatin was US$372,255. CINV lasts for about 5-7 days following chemotherapy administration and can be classified as an acute health condition. The use of QALYs to value morbidity for short-term condition such as CINV has both measurement and evaluation problems (Bala & Zarkin, 2000) which are explained in Chapter 2. The evaluation problem arises because the multiplicative product of the utility weights and life-years gained is extremely small leading to high cost per QALY estimates. Thus, CUA also may not be an appropriate economic evaluation method for determining the value of antiemetic regimens for prevention of CINV. Therefore, CBA where costs and benefits of the health care interventions are compared in monetary values is being proposed to be the most appropriate method for valuing antiemetic regimens for prevention of CINV, an acute health condition with significant impact on HRQOL.

In a CBA, benefits are measured in monetary values by determining the willingness-to-pay (WTP) for the outcomes due to the new health care intervention. Dranitsaris et al (2001b) conducted a multinational study to determine the WTP for improved emesis control due to NK-1 receptor antagonists, following cisplatin-based chemotherapy. The study showed that there were considerable differences in cancer patients' valuation of improved emetic control between countries. Thus it is necessary to evaluate the WTP for improved emetic control, specifically among patients in the United States. The study was conducted before the benefits of NK-1 receptor antagonists were established in randomized clinical trials. Now, WTP amounts can be determined for the actual benefit provided by the new antiemetic agents as results from phase III randomized clinical trials of NK-1 receptor antagonists are available. Though this study determined the WTP for improved emesis control, it was not used for further economic evaluation of the antiemetic regimens. Thus, it is necessary to determine the value of improved emesis control in the US and use those values in a cost-benefit study of new antiemetic regimens.

The current study is a comprehensive economic evaluation of antiemetic regimens for prevention of CINV following highly and moderately emetogenic chemotherapy. The current study conducted cost-effectiveness evaluations of new antiemetic regimens compared to the previous guidelines and clinical practice for prevention of CINV following chemotherapy. Cost-benefit analysis using the contingent valuation method was done to compare the new regimen to

the standard regimen for prevention of CINV following highly and moderately emetogenic chemotherapy.

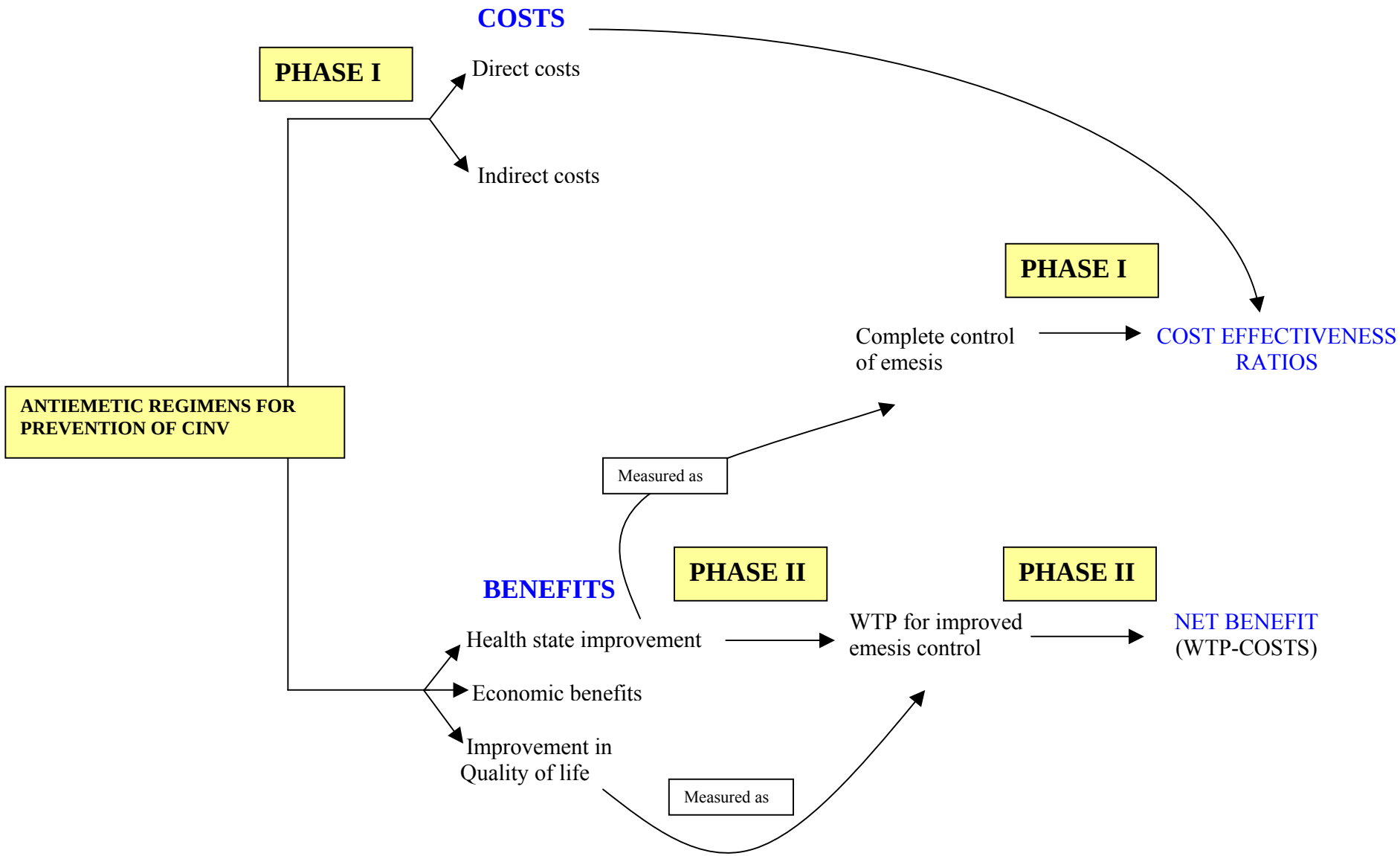
1.8: Research Objectives

1) What are the incremental costs and consequences of introducing the three-drug regimen (aprepitant in addition to the standard regimen) for prevention of CINV following HE regimen from the payer and societal perspective?
2) What are the incremental costs and consequences of introducing palonosetron for prevention of CINV following ME chemotherapy regimen from the payer and societal perspective?
3) What is the monetary value that patients place on improved emesis control due to the new antiemetic regimen for prevention of CINV due to HE chemotherapy?
4) What is the monetary value that patients place on improved emesis control due to the introduction of palonosetron as the new antiemetic regimen for prevention of CINV due to ME chemotherapy?

1.9: Conceptual Framework of the Study

The purpose of this study is to conduct a comprehensive economic evaluation of antiemetic agents for prevention of CINV. The study will be conducted in two phases. Figure 1-1 shows a schematic representation of the conceptual framework of the study. Phase I involves construction of a decision analytic model to compare the incremental costs and benefits associated with prophylactic antiemetic regimens for prevention of CINV. The incremental cost-effectiveness ratios (ICER) for the antiemetic regimens will also be determined in Phase I. Phase II will determine the monetary value that patients place on the improved emesis control due to the new antiemetic regimens for prevention of CINV following highly emetogenic and moderately emetogenic chemotherapy. Phase II also involves conducting cost-benefit analyses of the new antiemetic regimens using the monetary value of benefits determined by using the WTP methodology.

Figure 1-1: Conceptual Framework for Economic Evaluation of Prophylactic Antiemetic Regimens for Prevention of CINV



Phase I

CINV can be managed by different prophylactic antiemetic regimens and the challenge is to quantify the effects and identify the regimens that deliver maximum benefit in the most efficient manner. Phase I involves constructing two decision analytical models to systematically compare the different prophylactic antiemetic regimens for prevention of CINV due to HE and ME chemotherapy. The alternative antiemetic regimens are discussed in the section titled "Economics of Prevention of CINV" and later in Chapter 3, Methods. The CEA will be conducted from the payer and societal perspective.

A hypothetical cohort of patients with cancer who are receiving their first cycle of cisplatin-based HE chemotherapy will be considered for the HE model. Another hypothetical cohort of patients with cancer who are receiving their first cycle of ME chemotherapy such as cyclophosphamide, plus an anthracyclines such as doxorubicin, epirubicin etc. will be considered for the ME model. The cohorts will be tracked for a period of 5 days to coincide with the time period for which patients usually experience CINV during a cycle of chemotherapy and for which relevant clinical data from studies are available. For both HE and ME models, the primary outcomes of Phase I are 1) number of patients with complete control defined as no emesis and no rescue medications over the 5-day period and 2) costs.

The effectiveness of the various antiemetic regimens included in the models will be obtained from the published literature. The resource costs include cost of prophylactic antiemetic regimens, drug administration costs, cost of managing breakthrough emesis and indirect costs. The costs included for calculation of cost-effectiveness ratios will be based on the perspective of the analysis. The incremental cost per completely controlled patient will be calculated for each strategy relative to the next most costly strategy as the difference in the total costs of the two regimens divided by the difference in the effectiveness of the two regimens

$$\text{Incremental cost-effectiveness ratios (ICER)} = \frac{\Delta \text{ Total Costs}}{\Delta \text{ Effectiveness}}$$

The incremental analysis helps in determining if the additional benefit offered by the new regimen is worth the additional cost of delivering the intervention. To test the impact of

uncertainties in the effectiveness and cost parameters on the results, one way sensitivity analysis and probabilistic sensitivity analysis will be used.

Phase II

Phase II of the study involves using the contingent valuation (CV) method to determine the monetary value that patients place on improved emesis control due to the new regimens. The CV method is a direct measurement of WTP using a survey based measure to elicit monetary values by presenting hypothetical scenarios about the healthcare intervention under evaluation. The maximum WTP for improved emesis control is determined for two scenarios: improved emesis control due to addition of aprepitant to the standard regimen for prevention of CINV following HE chemotherapy and improved emesis control due to palonosetron for prevention of CINV due to ME chemotherapy. An ex-post/user-based perspective will be used to construct the CV survey. A payment card method will be used to determine the maximum WTP for the two scenarios. The study population will include patients above 18 years of age who are currently receiving their first or subsequent cycles of chemotherapy, or have received it within the past three months are and are able to understand and speak English.

Face to face interviews will be conducted with the patients who agree to participate in the study. In addition to the maximum WTP, information on age, gender, education, annual household income, number of members in the household, type of insurance, marital status, and employment status will be collected. The survey also elicits information about the level of importance placed on improved emesis control, preference of new versus the old regimens, reasons for the preference and level of difficulty in understanding and answering the WTP questions. The amount indicated by the respondents on the payment card was taken as the monetary value placed by the patients on improved emesis control. Multivariate semi-logarithmic regression models were used to assess the association between WTP amount and annual household income, which is also the method used to establish construct validity of the WTP survey.

The WTP amounts obtained using the CV method will be used to conduct CBA for the new regimens for prevention of CINV following HE and ME chemotherapy. The net benefit of the new regimens will be calculated as the difference between the incremental costs and incremental benefits of the new regimens compared to the standard regimens used for prevention of CINV.

1.10: Study Goals and Objectives

The overall goal of the study was to conduct a comprehensive economic evaluation of prophylactic antiemetic regimens for prevention of CINV following administration of HE and ME chemotherapy. The aim of the study was to determine the cost-effectiveness of new antiemetic regimens compared to the regimens recommended by previous guidelines and used in clinical practice. The study also involved determining the monetary value of improved emesis control offered by the new antiemetic regimens.

Objectives for Phase I

Objective 1.1:

To develop a decision analytical model that identifies the costs and effectiveness of alternative regimens for prevention of CINV in cancer patients receiving HE chemotherapy.

Objective 1.2:

To develop a decision analytical model that identifies the costs and effectiveness of alternative regimens for prevention of CINV in cancer patients receiving ME chemotherapy.

Objective 1.3:

To determine the incremental costs and benefits of using the new antiemetic regimen (aprepitant with standard regimen) versus the older regimens for prevention of CINV in cancer patients receiving HE chemotherapy.

Objective 1.4:

To determine the incremental costs and benefits of using the new antiemetic regimen (palonosetron) versus the older regimens for prevention of CINV in cancer patients receiving ME chemotherapy.

Objectives for Phase II

Objective 2.1:

To determine the monetary value that cancer patients place on improved emesis control due to addition of aprepitant to the standard regimen following HE chemotherapy using the CV method.

Objective 2.2:

To determine the monetary value that cancer patients place on improved emesis control with the introduction of palonosetron instead of the standard regimen following ME chemotherapy using the CV method.

Objective 2.3:

To determine the association between maximum WTP for improved emesis control following HE chemotherapy and respondents' demographic and clinical characteristics (age, gender, martial status, education, annual household income, number of members in the household, employment status, insurance status, type of cancer, previous experience of chemotherapy and previous experience of emesis due to chemotherapy).

Objective 2.4:

To determine the association between maximum WTP for improved emesis control following ME chemotherapy and respondents' demographic and clinical characteristics (age, gender, martial status, education, annual household income, number of members in the household, employment status, insurance status, type of cancer, previous experience of chemotherapy and previous experience of emesis due to chemotherapy).

Objective 2.5:

To conduct a CBA to estimate the net benefit of adding aprepitant to the standard regimen for prevention of CINV following HE chemotherapy.

Objective 2.6:

To conduct a CBA to estimate the net benefit of using palonosetron instead of the standard regimen for prevention of CINV following ME chemotherapy.

1.11: Significance of Study

The economics of prevention of CINV using antiemetic agents needs to be studied in the light of higher costs of the antiemetic drugs. Introduction of newer interventions in addition to the existing ones can threaten drug formulary budgets of third-party payers, hospitals and cancer centers. Consequently, there is a growing pressure to evaluate all new interventions before implementation. Clinical practice guidelines recommend the use of treatment strategies based on effectiveness of the intervention, which should be the primary requirement for its acceptance in health care. However, effectiveness alone is not a sufficient criterion to initiate services in most practical health care contexts, emphasizing the important role of the cost-effectiveness approach

in policy decisions. Thus, the study results will have relevance to different players in the health care sector, namely patients, physicians, hospitals, third party payers and society as a whole.

Society/policy makers

The results of the CEA and CBA analysis which combines information on health benefits, health risks and costs of health care services will assist informed policy decision making. The WTP estimates will provide important information about the value placed on CINV and improved emesis control due to new antiemetic agents. Willingness-to-pay can be used to calculate the benefit to cost ratio for comparing treatment of CINV with other health care interventions for resource allocation decisions.

Payers

Many policy decisions are made at the local levels namely the health plan, hospital or health maintenance organization (HMO) level. These policy decisions include inclusion of drugs on the local or regional formulary of the HMO or health plan. HMOs and managed care organizations (MCOs) can utilize the ICER to aid formulary decision making. The decision analytical models developed in this study can be applied to provide ICER for different subpopulations of specific managed card plans.

Health care professionals

The results will also have relevance to clinical decision-making. In clinical practice, physicians and other decision-makers can use the study results to determine whether costs associated with each antiemetic regimen are worth the benefits provided by the therapies. The study can also help physicians, other health care professionals and researchers in developing clinical practice guidelines, which incorporate not only benefits and risk but also costs of antiemetic therapy.

Hospitals

CEA/CBA results will have relevance to the hospital policy makers to determine the impact of new interventions on their formulary budgets. The study results will provide the incremental cost per successfully treated patient on new antiemetic regimen compared to standard regimen. Net benefit (WTP – Cost) is a more relevant outcome measure to the hospital policy makers to create a monetary rank order based on user value as new products are introduced into clinical practice.

Scientific literature

Finally, the study will be a valuable addition to the scientific literature in the field of supportive cancer care, pharmacoeconomics, and economic evaluation methodologies. In the

recent years, researchers have developed a renewed interest in CBA as a method for assessing the value of an intervention and WTP results from the study will be a timely contribution to the field.

CHAPTER TWO

LITERATURE REVIEW

2.1: Pathophysiology of Chemotherapy-Induced Nausea and Vomiting (CINV)

Chemotherapy-induced nausea and vomiting (CINV) are perceived among the most distressing and feared side effects of chemotherapy by patients with cancer (Boer-Dennert et al., 1997; Griffin et al., 1996). It is estimated that between 60-80% of cancer patients receiving chemotherapy experience nausea and/or vomiting if prophylactic antiemetic drugs are not used (DeVita et al., 2001; King, 1997).

The exact mechanism by which chemotherapy induces nausea and vomiting is not clearly understood. Different chemotherapy agents act on various sites and cause nausea and vomiting by diverse mechanisms of action (Stewart, 1991). Chemotherapy agents cause nausea and vomiting by direct or indirect activation of the chemoreceptor trigger zone (CTZ), peripheral stimulation of the gastrointestinal tract, direct cerebral activation, vestibular mechanisms and alterations of taste and smell. It is suggested that the most common mechanism is through the activation of the CTZ. The interaction between chemotherapy and the CTZ releases various neurotransmitters that activate the vomiting center (Berger & Clark-Snow, 2001). Some of the neurotransmitters released are dopamine, serotonin, histamine, and substance P (Bender et al., 2002). Though a single neurotransmitter is not responsible for all CINV, serotonin and 5-hydroxytryptamine (5-HT) play an important role in the pathophysiology of acute CINV. Substance P, another neurotransmitter found in the gastrointestinal tract and the CTZ of the area postrema, exerts its emetic effects by binding to a specific neuroreceptor, NK1 (Olver, 2004). Antiemetic agent, aprepitant exert its antiemetic effect by antagonism of the NK1 receptors and is found to have better antiemetic control during delayed CINV, compared to previous regimens.

Some terms associated with CINV and their definitions are presented in Table 2-1. CINV can be classified into five distinct syndromes based on the time of occurrence during a chemotherapy cycle (Bender et al., 2002; Navari, 2003). These five syndromes are described in Table 2-2.

Table 2-1: Chemotherapy-Induced Nausea and Vomiting Related Terms and Their Definitions

Terms	Definitions
Nausea	Nausea is a subjective, unobservable phenomenon of an unpleasant sensation experienced in the back of the throat and the epigastrium that may or may not culminate in vomiting.
Vomiting	Vomiting is the forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral/nasal cavity.
Retching	Retching is an associated phenomenon that is described as an attempt to vomit without bringing anything up.

Table 2-2: Chemotherapy-Induced Nausea and Vomiting Related Syndromes and Their Definitions

CINV Syndromes	Definitions
Acute CINV	Occurs within the first 24 hours after administration of chemotherapy.
Delayed CINV	Defined as nausea and vomiting occurring more than 24 hours (days two to seven of chemotherapy cycle) after the administration of emetogenic chemotherapy (Kris et al., 1985; Tavorath & Hesketh, 1996).
Anticipatory CINV	Occurs within one week prior to the actual administration of chemotherapy and is linked to repeated associations with chemotherapy side effects and environmental stimuli. For example, certain tastes, sensations, smells, or even thoughts experienced by patients who receive chemotherapy may evoke nausea and/or vomiting.
Breakthrough CINV	Occurs either in the acute or delayed phases of emesis, in spite of patients being treated with prophylactic antiemetic therapy. Rescue therapy is usually administered to control breakthrough CINV.
Refractory CINV	Occurs during subsequent cycles of chemotherapy when antiemetic prophylaxis or rescue therapy has failed in earlier cycles.

2.2: Factors Associated with Increased Risk of CINV

A number of patient, disease and treatment-related characteristics have been identified as potential factors associated with increased risk of nausea and vomiting following chemotherapy. These factors are important for developing antiemetic treatment guidelines and tailoring antiemetic regimens to achieve the maximum emetic control in patients receiving chemotherapy.

Disease and Treatment-related Factors

Emetogenicity of the Chemotherapy Agents

The *emetogenic potential of the chemotherapy agent*, defined, as the intrinsic capacity of a chemotherapy agent to produce an emetic episode in a patient who is receiving the agent, is the most important predictor of CINV (Lindley, Bernard, & Fields, 1989; Osoba et al., 1997a; Pater et al., 1994). Hesketh et al. (Hesketh, 1999; Hesketh et al., 1997) and the expert consensus by the American Society of Health-System Pharmacists (ASHP) (ASHP, 1999) have classified the available chemotherapy agents into five levels of emetogenicity based on the proportion of patients who experience acute emesis in absence of effective antiemetic prophylaxis. Table 2-3 shows the classification of single chemotherapy agents into the various levels based on their emetogenicity. Chemotherapy agents in level 5 are termed as highly emetogenic (HE) chemotherapy and regimens with cisplatin are specifically termed as cisplatin-based HE chemotherapy. Chemotherapy agents classified under levels 3 and 4 are termed as moderately emetogenic (ME) chemotherapy. The chemotherapy agents that fall under levels 1 and 2 have low potential of causing CINV.

For combination chemotherapy regimens, the level of emetogenicity is determined based on an algorithm which combines the emetogenicity of the single agents (DeVita et al., 2001; Hesketh et al., 1997). Table 2-4 describes the algorithm used to calculate the emetogenicity of combination chemotherapy.

Table 2-3: Classification of Emetogenicity of Single Chemotherapy Agents

Level	Frequency of Acute Emesis (%)*	Chemotherapy Agents
5	> 90 %	Carmustine > 250 mg/m^2
		Cisplatin ≥ 50 mg/m^2
		Cyclophosphamide > 1,500 mg/m^2
		Dacarbazine
		Mechlorethamine
		Streptozotocin
4	60-90 %	Amifostine > 500 mg/m^2
		Busulfan > 4mg/d
		Carboplatin
		Carmustine < 250 mg/m^2
		Cisplatin < 50mg/m^2
		Cyclophosphamide >750 ≤ 1,500 mg/m^2
		Cytarabine ≥ 1g/m^2
		Doxorubicin > 60 mg/m^2
		Epirubicin > 90 mg/m^2
		Melphalan > 50 mg/m^2
		Methotrexate > 1,000 mg/m^2
		Procarbazine (oral)
3	30-60 %	Cyclophosphamide ≤ 750 mg/m^2
		Cyclophosphamide (oral)
		Doxorubicin 20-60 mg/m^2
		Epirubicin ≤ 90 mg/m^2
		Hexamethylmelamine (oral)
		Idarubicin
		Ifosfamide
		Irinotecan
		Methotrexate 250-1000 mg/m^2
		Mitoxantrone < 15 mg/m^2

* Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

Table 2-3 (Continued): Classification of Emetogenicity of Single Chemotherapy Agents

Level	Frequency of Acute Emesis (%)*	Chemotherapy Agents
2	10-30%	Capecitabine
		Cytarabine 100-200 mg/m^2
		Docetaxel
		Etoposide
		5-Fluorouracil < 1000 mg/m^2
		Gemcitabine
		Methotrexate > 50 mg/m^2 < 250 mg/m^2
		Mitomycin
		Paclitaxel
		Topotecan
1	< 10%	Alpha Interferon
		Bleomycin
		Chlorambucil (oral)
		Dexrazoxane
		Fludarabine
		Gemtuzumab
		Hydroxyurea
		Imatinib
		Methotrexate ≤ 50 mg/m^2
		Rituximab
		Vinblastine
		Vincristine
		Vinorelbine

* Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

Table 2-4: Algorithm for Determining Emetogenicity of Combination Chemotherapy Regimens

TO DETERMINE THE LEVEL OF EMETOGENICITY OF THE COMBINATION REGIMEN:
First identify the drug in the combination regimen with the highest emetic potential based on the Hesketh classification. To this level add the emetogenic potential of other drugs in the regimen based on the following:
1. Level 1 agent does not add to the emetogenic potential of the combination regimen.
2. One or more agents of level 2 in the combination regimen will increase the emetic potential by 1 level.
3. Each agent of level 3 or 4 in the combination regimen will increase the emetic potential by 1 level, with maximum level reaching level 5.

For a classification schema to be more relevant and serve as a basis for treatment recommendations, it must also account for the ability of certain chemotherapy agents to produce delayed emesis. The potential for a chemotherapy agent to cause delayed emesis is proportionate to its ability to cause acute emesis. In the absence of prophylaxis for delayed emesis, the incidence of delayed emesis is 60-90% in patients treated with cisplatin and 20-33% in those receiving carboplatin, cyclophosphamide or doxorubicin (Gralla, 1997; Gralla et al., 1999; Hesketh, 1999). Though emesis in the acute phase is a strong predictor for incidence of delayed emesis, 40% of patients suffer from delayed emesis despite complete protection in the acute phase (de Wit, 2003). Individual risk assessment is imperative and because chemotherapy is most commonly administered in cycles over a period of time, it is also important that assessment be maintained throughout the treatment period.

Previous Exposure to Emetogenic Chemotherapy

Patients with uncontrolled emesis in earlier cycles of chemotherapy are more likely to experience emesis in subsequent cycles in spite of prophylactic antiemetic administration. Poorly controlled nausea and vomiting in previous cycles also increases the likelihood of anticipatory nausea and vomiting.

Other Possible Disease-related Factors

Performance status (as measured by the European Cooperative Oncology Group (ECOG) Performance Status Scale), tumor burden and stage of disease may be associated with incidence of CINV. The ECOG performance status scale is used to assess how a cancer patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (Oken et al., 1982). The assessment is conducted on a scale of 0-5 where 0 indicates that the patient is fully active, and able to carry on all activities without restriction. A score of 5 on the scale indicated death. Osoba et al. (Osoba et al., 1997a) found that 57% of patients with a ECOG performance status of either 1 or 2 experienced CINV compared to 49% of patients with ECOG performance status of 0 or normal. A large tumor burden especially in patients with ovarian cancer or abdominal malignancies also may increase the likelihood of experiencing emesis (Doherty, 1999). A prospective longitudinal study designed to study factors predicting development of CINV in Chinese breast cancer patients receiving moderately emetogenic chemotherapy found that later stage of disease increased the

risk of longer duration of acute nausea and greater frequency of acute nausea and vomiting (Molassiotis, Yam, Yung, Chan, & Mok, 2002).

Patient-related Factors

Patient-related factors such as age, gender, history of alcohol use, motion sickness, previous exposure to chemotherapy, and prior experience of emesis may increase or decrease the risk of developing CINV (Doherty, 1999; Osoba et al., 1997a). Elderly patients tend to tolerate chemotherapy better than younger patients. Women, younger than 50 years of age require aggressive antiemetic regimens since they are more likely to experience nausea and vomiting compared to men. Patients with prior history of emesis during pregnancy or due to motion sickness are also at an increased risk of experiencing CINV. In patients receiving cisplatin, those who have a history of chronic alcohol ingestion, greater than 100g/day (approximately five alcoholic beverages per day) appear to experience less intense nausea and vomiting (Goodman, 1997).

Certain psychosocial and behavioral factors such as stress, negative attitude towards chemotherapy (Tsavaris et al., 2000), anxiety (Molassiotis et al., 2002) and pretreatment expectations of nausea and vomiting (Andrykowski et al., 1988; Jacobsen et al., 1988; Roscoe, Hickok, & Morrow, 2000) may also lead to increased risk of emesis.

Factors Specifically Associated with Increased Risk of Delayed CINV

The level of protection achieved in the acute phase of the first chemotherapy cycle is a very important prognostic factor for incidence of delayed emesis in the same and subsequent chemotherapy cycles (IGAR, 1994). Independent of the type of antiemetic treatment received for acute or delayed emesis, complete protection from nausea and vomiting in the acute phase significantly reduces the risk of developing emesis in the delayed phase (Schnell, 2003). Delayed CINV is more frequently seen in patients receiving HE chemotherapy. Some other possible factors associated with increased risk of delayed emesis include cisplatin > 90mg/m^2, younger age, female gender, and larger tumor burden (Roila et al., 2002).

It is important to identify the prognostic or risk factors that predict the likelihood of cancer patients developing acute, delayed and anticipatory CINV. These factors will aid in

developing a risk profile for the patients at the greatest risk of CINV and tailor antiemetic regimens for prevention of CINV based on individual risk profile.

2.3: Prevention Strategies for CINV

The most important point about managing CINV is that preventing CINV is more effective than treating it (Markman, 2002). Antiemetic agents administered before chemotherapy are effective in reducing the incidence of acute emesis, but it is difficult to completely control CINV once it has begun. One of the goals of antiemetic therapy is to achieve complete control in all settings, beginning with the initial cycle of chemotherapy, thus improving patient compliance, quality of life, and preventing development of anticipatory and refractory nausea and vomiting during subsequent cycles of chemotherapy. The other goals of antiemetic therapy are to provide maximum convenience for patients and staff, to eliminate potential side effects of the agents, and to minimize the cost of treatment of CINV (Berger & Clark-Snow, 2001). Inappropriate control of acute emesis leads to breakthrough, delayed, refractory and anticipatory emesis in the same and subsequent chemotherapy cycles.

The currently available antiemetic agents have not been adequately tested for breakthrough, refractory and anticipatory emesis (King, 1997). In addition to pharmacological interventions, nonpharmacologic interventions can be used to prevent anticipatory nausea and vomiting or control CINV. Nonpharmacologic interventions are "techniques that unite the mind and body by using psychologic interventions to control physiologic responses" (Bender et al., 2002; King, 1997). These include behavioral interventions, such as relaxation, self-hypnosis, cognitive distraction, acupuncture, acupressure and music therapy (Bender et al., 2002; King, 1997). Since the focus of the study is the use of pharmacological interventions, nonpharmacological interventions will not be discussed.

Assessment of Efficacy of Antiemetic Agents

Vomiting or emesis can be assessed by calculating the number of emetic episodes experienced by patients each day during the period of interest, usually 5-7 days. The percentage of patients with no emetic episode (with or without nausea) during the acute, delayed and overall phase is the primary outcome measure for control of emesis (Kris et al., 2005). The gold standard for determining the efficacy of antiemetic agents is the complete prevention of all

emesis and nausea (Hesketh, Gralla, du, & Tonato, 1998). It is suggested that control of emesis and nausea should be reported separately due to the subjective nature of nausea. The assessment of intensity of nausea is measured using visual analog scales (VAS) or descriptive ordinal scales. A four-point descriptive ordinal scale measuring intensity of nausea as none, mild, moderate, and severe has been found to have a high correlation with a VAS (Hesketh et al., 1998).

A more stringent criterion for determining the efficacy of antiemetic agents is total control – complete control of both emesis and nausea. In clinical trials, complete control of nausea was approximately 10% lower compared to complete control of emesis (Hesketh et al., 1998). Thus, when 'total control' is used as an outcome measure, the total control rates are reported to be very similar to the complete control rates of nausea. Also, nausea and vomiting depend on different pathophysiological mechanisms and thus they should be separately evaluated in clinical trials. Other secondary measures include complete protection, defined as proportion of patients with minimal or no nausea, no vomiting or retching and no use of rescue medication in the post-chemotherapy period. Outcome measures based on the number of emetic episodes: major control (< 3 emetic episode), minor control (3-5 emetic episodes) and failure (> 5 emetic episodes), are also sometimes reported in clinical trials.

Pharmacotherapy for Prevention of CINV

Various classes of drugs such as phenothiazines, butryophenones, substituted benzamides, cannabinoids, steroids and 5-HT_3 receptor antagonists (5-HT_3 RA) are available to control the incidence of CINV (Gralla, 1997). Some older classes of drugs such as phenothiazines, benzodiazepines and butyrophenones are used as rescue medications for breakthrough emesis. Newer antiemetic agents such as aprepitant and palonosetron have been introduced recently.

Older Antiemetic Agents

A) Phenothiazines (Phenergan®, Compazine®)

Phenothiazines such as prochlorperazine, promethazine and thiethylperazine block the vomiting impulses by antagonizing the dopamine receptors (Flake, Scalley, & Bailey, 2004). These agents have tranquilizing and antiemetic effects and are used in combination antiemetic regimens for prevention of nausea and vomiting due to mildly emetogenic chemotherapy (Goodman, 1997). Phenothiazines are also given as rescue medications for breakthrough nausea

and vomiting. Phenothiazines may increase risk of extrapyramidal symptoms, especially in patients aged 30 years or younger (Goodman, 1997). Some other common side effects include sedation, lethargy and skin sensitization (ASHP, 1999).

B) Butyrophenones (Haldol®)

Butyrophenones are major tranquilizers but are less effective in preventing nausea and vomiting compared to other antiemetics such as 5-HT_3 RA. But these agents are particularly useful when anxiety and anticipatory symptoms aggravate the degree and intensity of nausea and vomiting. Butyrophenones such as haloperidol and droperidol may be used in combination with 5-HT_3 RA. However, adverse effects such as extrapyramidal symptoms, and dystonic reactions can be severe with butyrophenones (Goodman, 1997).

C) Substituted Benzamides

Substituted benzamides such as metoclopramide in high dosages were found to effectively block 5-HT_3 receptors and were widely used for preventing CINV. But high doses of metoclopramide can cause extrapyramidal symptoms in up to 5% of patients (Schnell, 2003). With the advent of 5-HT_3 RA which are more effective and less toxic in prevention of cisplatin-induced emesis, metoclopramide is now used only in combination with other antiemetic agents or as rescue medication for breakthrough emesis (Goodman, 1997; NCCN, 2005). Some guidelines recommend oral metoclopramide in combination with corticosteroids for prevention of delayed emesis due to HE and ME chemotherapy (Gralla et al., 1999; NCCN, 2005). The dose of metoclopramide ranges from 20mg and 40mg to be given two to four times a day for three or four days for control of delayed CINV.

D) Benzodiazepines

Benzodiazepines such as lorazepam and diazepam may have an antiemetic effect due to their anxiolytic and amnesic effects. The temporary amnesic effects of benzodiazepines make it useful in patients who suffer anticipatory nausea and vomiting and the anxiolytic effects make it useful in patients awaiting their first chemotherapy. It was found that lorazepam reduced the incidence of anticipatory nausea and vomiting and acute emesis induced by cisplatin (Malik et al., 1995). These agents have little antiemetic efficacy as single agents and are recommended as adjuncts to other antiemetics (DeVita et al., 2001).

E) Cannabinoids

Cannabinoids such as dronabinol can be used as an option in patients with CINV which is refractory to conventional antiemetic treatment and as an adjuvant to other antiemetics. This class of drugs may be useful in younger patients without cardiac or psychiatric illness and/or in patients who are sensitive to phenothiazines (Goodman, 1997). Some common side effects of dronabinol include drowsiness, euphoria and vision difficulties (ASHP, 1999).

F) Corticosteroids

Corticosteroids are effective as single agents or in combination for prevention of CINV. Dexamethasone is the most widely studied corticosteroid and is an effective, convenient and inexpensive anti-emetic useful in both acute and delayed emesis with chemotherapy of mild, moderate and severe emetic potential. A meta-analysis of randomized clinical trials showed that single agent dexamethasone was significantly superior to placebo or no treatment in complete control of acute and delayed CINV among patients receiving different types of chemotherapy regimens (Ioannidis, Hesketh, & Lau, 2000). The pooled results of three studies comparing dexamethasone to metoclopramide showed that the former provided better control of acute CINV (Ioannidis et al., 2000). In patients receiving cyclophosphamide or anthracycline-based chemotherapy, dexamethasone has been shown to be equal or superior to metoclopramide or equal to 5-HT_3 RAs (Herrstedt et al., 2005) in providing acute antiemetic control.

As an antiemetic, dexamethasone has been administered in doses ranging from 4 mg to 20 mg for a period of one to five days for prevention of acute and delayed CINV following highly emetogenic and moderately emetogenic chemotherapy. A comparison study of intravenous (IV) dexamethasone in dosages ranging from 4 mg to 20 mg to control acute emesis was conducted among patients receiving cisplatin-based chemotherapy (IGAR, 1998a). The study results showed that a single 20 mg IV dose before chemotherapy was considered as the most efficacious dose for prevention of acute cisplatin-induced acute emesis. In another randomized, double-blind clinical trial to determine optimum dose of IV dexamethasone in patients receiving ME chemotherapy such as anthracyclines, carboplatin or cyclophosphamide, a single dose of 8 mg was recommended as sufficient for acute control of emesis (IGAR, 2004).

Though single agent dexamethasone is effective in controlling emesis in patients receiving ME chemotherapy and low doses of cisplatin, it is ineffective for patients receiving higher doses of cisplatin (Herrstedt, 2004). Since corticosteroids improve the antiemetic effects of other antiemetics, they are ideal drugs for use in combination chemotherapy. Dexamethasone,

in combination with 5-HT_3RAs showed increased effectiveness in prevention of acute CINV following administration of both HE and ME chemotherapy (Joss et al., 1994). Continuous use of corticosteroids for a period of four to five days may cause adverse effects such as insomnia, anxiety, or euphoria (Goodman, 1997).

G) 5-HT_3 receptor antagonists (5-HT_3 RAs)

Due to its high efficacy and favorable toxicity profile compared to other antiemetic agents, 5-HT_3RAs are currently the first-line agents and the gold standard for prevention of CINV in patients receiving HE or ME chemotherapy (Gralla et al., 1999; Schnell, 2003). The 5-HT_3RAs specifically prevent the binding of the neurotransmitter, serotonin to the 5- HT_3 receptors on the vagal nerves that trigger the emetic response. Due to the specific nature of its binding, it precludes the severe and distressing side effects associated with conventional antiemetics such as metoclopramide. The 5-HT_3RAs provide complete acute antiemetic protection, i.e. no nausea, no vomiting and no use of rescue medications in 40-60% of patients receiving cisplatin based chemotherapy and 60-80% of patients receiving ME chemotherapy (Schnell, 2003). In patients receiving high-dose cisplatin-based chemotherapy regimens, 5-HT_3RAs provide complete antiemetic protection in the acute phase in 25-60% of patients (Audhuy et al., 1996; Beck et al., 1992; Hesketh et al., 1996; Marty et al., 1995; Navari et al., 1995).

Three 5-HT_3 RAs are currently available in the United States for prevention of emesis: dolasetron (Anzemet®), granisetron (Kytril®) and ondansetron (Zofran®). All three agents are available in both injectable and oral formulations. The injectable formulations of all three agents are indicated for use with highly and moderately emetogenic chemotherapy, whereas only the oral route of granisetron and ondansetron are indicated for use with highly emetogenic chemotherapy. Oral administration of a 5-HT_3RA and dexamethasone provide similar clinical outcomes as IV administration. The administration of 5-HT_3 RAs by the oral route is recommended whenever appropriate if the gastrointestinal tract is intact and compliance is assured. Studies have also shown that the oral dosage form of 5-HT_3 RA have equivalent efficacy to its intravenous form (Berger & Clark-Snow, 2001). Several randomized, controlled studies have shown that ondansetron, granisetron and dolasetron have equivalent complete control rates, defined as complete absence of nausea or vomiting, among patients on HE or ME chemotherapy (Berger & Clark-Snow, 2001; Gralla et al., 1998; Hesketh, 2000). For the purpose

of this study, ondansetron is used as representative of the 5-HT_3RA class of antiemetics and is discussed below in detail.

Ondansetron (Zofran®)

a) For Highly Emetogenic Chemotherapy

Ondansetron was the first 5-HT_3RA to be approved in the US for prevention of nausea and vomiting in patients receiving chemotherapy. There is conflicting data regarding the single optimal dose of ondansetron for prevention of acute emesis from cisplatin. A study by Beck and colleagues, comparing various doses of ondansetron for prevention of acute CINV showed that 32 mg dose was superior to 8 mg, particularly in patients receiving high dose cisplatin (> 100mg/m^2) (Beck et al., 1992). However, in another study, Seynaeve and colleagues showed that a single dose of 8 mg was equally effective to a 32 mg dose for prevention of acute emesis from cisplatin (Seynaeve et al., 1992). A number of other studies show results that support the equivalent efficacy of 8 mg dose to 32 mg dose of ondansetron (IGAR, 1995b). There are also controversies regarding the single vs. multiple administration of ondansetron for prevention of acute emesis following cisplatin. Clinical trial results suggest that increasing the number of doses does not improve efficacy and multiple-dose administration does not improve outcomes (Hesketh et al., 1996; Seynaeve et al., 1992). The study by Beck and colleagues also showed that a single IV dose of ondansetron was as effective as multiple dosing regimen of ondansetron (Beck et al., 1992).

Based on the results of a recent systematic literature review, the dosing recommendations of ondansetron for prevention of acute nausea and vomiting due to high emetic risk chemotherapy is a single oral dose of 24mg of ondansetron or single IV dose of 8mg (Jordan, Kasper, & Schmoll, 2005; M. G. Kris et al., 2005).

b) For Moderately Emetogenic Chemotherapy

For ME chemotherapy, the recommended adult oral dose of ondansetron is a single dose of 8 mg. For delayed emesis following ME chemotherapy, one 8 mg ondansetron tablet can be administered twice a day for 1-2 days following chemotherapy (ZOFRAN Prescribing Information Monograph). But dosing recommendations are not without controversy, and based on literature search, Herrstedt and colleagues have recommended 8 mg tablets twice daily for acute emesis or one single 8 mg IV dose of ondansetron (Herrstedt et al., 2005). There are no

randomized controlled studies to compare a single oral dose of ondansetron to a multiple dosing regimen for prevention of CINV following administration of ME chemotherapy.

For Prevention of Delayed CINV

The dosing regimen of ondansetron for prevention of delayed CINV due to HE and ME chemotherapy is not clearly outlined. It is seen from various randomized clinical trials with uniform antiemetic prophylaxis of the acute phase, that the control of cisplatin-induced delayed emesis with single agent 5-HT_3RAs is not significantly different than placebo (Gandara, Harvey, Monaghan, Perez, & Hesketh, 1993; Pater et al., 1997; Smyth, 1992). The efficacy of single agent granisetron compared to placebo for delayed emesis due to HE chemotherapy has been studied in 533 patients receiving cisplatin. In the delayed phase, the patients were randomized to receive either placebo or one of three doses (2.5mg, 5mg or 10mg) of oral granisetron twice a day until day seven after chemotherapy. The study results reported no significant differences in the efficacy of delayed emetic control among the various groups (Smyth, 1992). Thus, this suggests that as single agents, 5-HT_3RAs have minimal to modest activity against cisplatin-induced delayed emesis (Gandara et al., 1993; Kris et al., 2005).

Antiemetic Efficacy for Multiple Cycles of Chemotherapy

The emesis protection provided by the combination regimen of 5-HT_3RAs and dexamethasone decreases with each subsequent cycles of chemotherapy (de Wit et al., 1996; de Wit et al., 1998). A study conducted among 125 patients receiving six cycles of cisplatin-based chemotherapy reported that the antiemetic efficacy provided by combination of granisetron and dexamethasone decreased over subsequent cycles of chemotherapy. The initial complete acute emesis protection decreased from 66% to 39% in the sixth cycle and initial delayed emesis protection decreased from 52% to 43% in the sixth cycle (de Wit et al., 1996; de Wit et al., 1998).

Side Effects of 5-HT_3RA

Reports of clinical trial results and practical clinical experience showed that 5-HT_3 RAs are well-tolerated (Hesketh, 2000). There are no significant differences in the side effect profile of ondansetron, granisetron and dolasetron (Anastasia, 2000). The most common adverse events reported for all three 5-HT_3 RAs are headache, constipation and diarrhea (Audhuy et al., 1996; Bleiberg, Spielmann, Falkson, & Romain, 1995; Ettinger et al., 1996; Gralla et al., 1998). They

do not produce the extrapyramidal symptoms associated with dopaminergic antagonists such as metoclopramide. Other adverse events include transient changes in the blood pressure and clinically asymptomatic changes in the electrocardiographic parameters (Audhuy et al., 1996; Hesketh et al., 1996; Plosker & Goa, 1991). Transient changes in blood pressure resolve without treatment and are considered clinically insignificant.

New Antiemetic Agents

H) Aprepitant (Brand Name: Emend®)

Aprepitant is the first oral selective nonpeptide neurokinin (NK-1) receptor antagonist indicated for use in combination with a 5-HT_3 RA and corticosteroid for prevention of acute and delayed emesis due to HE chemotherapy regimens. Aprepitant prevents substance P from binding to the NK-1 receptors in the brain stem and thus resulting in inhibition of emesis (Bountra et al., 1996; Dando & Perry, 2004). Although aprepitant is more efficacious, the 2005 average wholesale price (AWP) of $309.00 for a three-day regimen makes it expensive compared to the other antiemetic agents used for prevention of acute and delayed emesis following administration of HE chemotherapy.

a) For Highly Emetogenic Chemotherapy

Two large phase III clinical trials have been conducted to determine the antiemetic efficacy of aprepitant in patients receiving high-dose cisplatin ($\geq$70mg/m^2) (Hesketh et al., 2003; Poli-Bigelli et al., 2003). One group of patients received standard antiemetic therapy consisting of IV ondansetron 32 mg and oral dexamethasone 20 mg on day one and oral dexamethasone 8 mg twice daily on day two to four. The other group received oral aprepitant 125 mg in addition to the standard therapy on day one and aprepitant 80 mg and oral dexamethasone 8 mg on days two and three and oral dexamethasone 8 mg on day four. The overall complete response (no emesis and no use of rescue therapy) rates reported in the two clinical trials were 62.7% and 72.7% for the aprepitant group compared to 43.3% and 52.3% of the standard regimen group. Complete response rates in the delayed phase were achieved in 67.7% and 75.4% of patients in the aprepitant group compared to 46.8% and 55.8% in the standard regimen group. These results show the superior efficacy of the aprepitant-based regimen in control of acute and delayed CINV compared to the standard regimen.

b) For Moderately Emetogenic Chemotherapy

Randomized clinical trials assessing efficacy of aprepitant in prevention of CINV following moderately emetogenic chemotherapy have been recently published. Warr and colleagues conducted a study among 857 chemotherapy naïve breast cancer patients receiving cyclophosphamide and either doxorubicin or epirubicin (Warr et al., 2005). The standard regimen group received two doses of 8 mg oral ondansetron on days one to three and 20 mg oral dexamethasone on day one. The aprepitant group received 125 mg of oral aprepitant, 8 mg of oral ondansetron twice daily, and 12 mg oral dexamethasone on day one. The aprepitant group also received 80 mg oral aprepitant on days two and three. The study results showed that compared to the standard regimen, more patients in the aprepitant group reported complete response during the acute phase, delayed phase and the overall study period. Thus, aprepitant added to the standard regimen has demonstrated better control of CINV compared to the standard regimen in patients receiving ME chemotherapy.

c) For Multiple Cycles of Chemotherapy

The antiemetic efficacy of aprepitant in addition to the standard regimen for prevention of CINV due to HE chemotherapy has been found to be sustained over multiple cycles of chemotherapy (de Wit et al., 2003; de Wit et al., 2004). De Wit and colleagues reported results from pooled analysis of multiple-cycle extensions of two large phase III aprepitant clinical trials (de Wit et al., 2003; de Wit et al., 2004). Chemotherapy naïve cancer patients receiving their first cycle of cisplatin were randomized to either the standard regimen group: IV ondansetron 32 mg and dexamethasone 20 mg on day one, dexamethasone 8 mg twice daily on days two to four, or aprepitant group: aprepitant 125 mg, IV ondansetron 32 mg, dexamethasone 12 mg on day one, aprepitant 80 mg on day two and three and dexamethasone 8 mg on days two to four. The patients received these regimens for six cycles and the end point of no emesis and no significant nausea was assessed for each cycle. A cumulative probabilities approach incorporating a model for transitional probabilities was used to analyze the data. The results showed that the estimated rates of no emesis and no significant nausea was higher for the aprepitant group compared to the standard group for all cycles of chemotherapy.

d) For Breakthrough CINV

Aprepitant has not been shown to mitigate ongoing emetic symptoms and has not been tested for continuous use for duration greater than five days in patients receiving emetogenic

chemotherapy. It should not be used to treat established nausea and vomiting regardless of its etiology and should not be prescribed on a PRN basis (Kohler & Hughes, 2003).

e) Adverse effects

The most common adverse events that occurred more frequently in the aprepitant group compared to the standard group include: asthenia/fatigue, dizziness, diarrhea, cough and hiccups (Hesketh et al., 2003; Poli-Bigelli et al., 2003).

I) Palonosetron (Brand Name: Aloxi®)

Palonosetron is a 5-HT_3 RA available as an injectable antiemetic agent. Palonosetron differs from older 5-HT_3 RAs since it has a higher binding affinity to the 5-HT_3 receptors, higher potency and a longer half-life. It is indicated for prevention of acute emesis due to HE regimens and prevention of acute and delayed emesis due to ME regimens. In the US, the recommended dose of palonosetron for the prevention of CINV is a single IV infusion of 0.25 mg approximately 30 minutes before the start of chemotherapy. Compared to other 5-HT_3RAs, palonosetron provides convenience for prevention of emesis due to its single dose schedule. The 2005 AWP of a 0.25mg 5 ml single dose vial is $340.20.

a) For Highly Emetogenic Chemotherapy

Currently for patients receiving HE chemotherapy, palonosetron has only been indicated for prevention of acute CINV. In a study of 650 patients receiving HE chemotherapy, two doses (0.25 mg or 0.75 mg) of palonosetron were compared to a single 32 mg dose of ondansetron. The study results showed no differences in the acute or delayed complete response rates between the three study groups. Thus, it can be concluded that a single 0.25 mg IV dose of palonosetron was at least as effective as a 32 mg IV dose of ondansetron for acute and delayed emesis following HE chemotherapy (Aapro, Bertoli, Lordick, Bogdanova, & Macciocchi, 2003). Studies comparing palonosetron to other regimens for prevention of acute and delayed CINV due to HE chemotherapy are currently lacking. More clinical trials of combination antiemetic regimens with palonosetron need to be carried out to establish whether it is more efficacious than the combination of corticosteroid with either metoclopramide or a 5-HT_3 RA for protection of delayed emesis due to HE chemotherapy.

b) For Moderately Emetogenic Chemotherapy

The efficacy of palonosetron as part of various different regimens has been extensively studied in patients receiving ME chemotherapy. The results from a study conducted among 569 patients receiving ME chemotherapy showed that a 0.25 mg IV dose of palonosetron provided significantly higher antiemetic control compared to a single 100 mg IV dose of dolasetron (Eisenberg et al., 2003). The study results showed that the single dose of palonosetron is as effective as a single dose of dolasetron in preventing acute CINV but the former regimen provides better emetic control in the delayed phase. In the delayed phase, approximately 57% of patients who received palonosetron reported achieving complete response as compared to 39% of patients who received dolasetron.

Gralla and colleagues conducted a multicenter, randomized, double blind study to compare two doses (0.25 mg or 0.75 mg) of IV palonosetron and a single IV dose of 32 mg ondansetron among 570 patients receiving ME chemotherapy (Gralla et al., 2003). The results indicated that a single IV dose of palonosetron provided significantly higher acute and delayed emetic control compared to a single IV dose of ondansetron. A phase II open label study was conducted to determine the efficacy of a single dose of palonosetron combined with a three-day regimen of aprepitant to prevent CINV in patients receiving moderately to moderately-high emetogenic chemotherapy. The preliminary results of the study showed that the combination was safe and may improve the overall prevention of CINV (Grote et al., 2004).

c) For Multiple Cycles of Chemotherapy

To date, only one noncomparative trial has been conducted to evaluate the efficacy of palonosetron in preventing CINV over repeated cycles of moderately to highly emetogenic chemotherapy (Cartmell et al., 2003). A single 0.75 mg IV dose of palonosetron with or without corticosteroids was given to the participants. The results showed that the efficacy of palonosetron was maintained during acute, delayed and overall phases during four cycles of chemotherapy (Cartmell et al., 2003).

d) Adverse Effects

The side effect profile of palonosetron is similar to that of the other 5-HT_3RAs with headache and constipation being among the most frequently reported side effects in clinical trials (Eisenberg et al., 2003; Gralla et al., 2003). Other serious side effects occur with a very low frequency and were similar in the palonosetron and the comparator group.

Combination antiemetic regimens and Recommendations for Antiemetic Use

Combination of two or more antiemetic agents provides better efficacy in prevention of CINV following administration of HE and ME chemotherapy than use of a single antiemetic agent. Several professional organizations such as the Multinational Association of Supportive Cancer Care (MASCC), the American Society of Clinical Oncology (ASCO), the American Society of Health-System Pharmacists (ASHP), the National Comprehensive Cancer Network (NCCN), and the Canadian Medical Association have published guidelines and evidence-based recommendations for the use of antiemetics in management of CINV (ASHP, 1999; ESMO, 2001; Gralla et al., 1999; MASCC, 1998; NCCN, 1997).

Highly Emetogenic Chemotherapy

Acute Phase

Several randomized double-blind clinical trials have been conducted to compare single agent 5-HT_3RA with a combination of 5-HT_3 RA and dexamethasone for prevention of CINV in patients receiving HE chemotherapy (Heron, Goedhals, Jordaan, Cunningham, & Cedar, 1994; IGAR, 1995a; Latreille et al., 1995; Olver et al., 1996). The results from these studies have unequivocally shown that the combination of a 5-HT_3 RA and dexamethasone provides superior antiemetic efficacy in the acute phase compared to 5-HT_3 RA alone. Thus, previous guidelines have recommended a combination of 5-HT_3 RA and corticosteroids before chemotherapy for control of acute emesis in patients receiving HE chemotherapy regimens (ASHP, 1999; Gralla et al., 1999).

Based on the results of randomized clinical trials (Chawla et al., 2003; Hesketh et al., 2003; Poli-Bigelli et al., 2003), new guidelines from the MASCC and the NCCN now recommend a triple combination of aprepitant, a 5-HT_3RA and dexamethasone for prevention of acute emesis due to HE chemotherapy (MASCC, 2004; NCCN, 2005). The use of palonosetron as a part of the triple combination regimen with aprepitant and dexamethasone has been recommended for prevention of acute emesis by the NCCN 2005 guidelines (NCCN, 2005). Though this regimen is a part of the new recommendations, randomized, double blind clinical trials determining its efficacy as compared to the triple combination regimen containing other 5-HT_3RAs have not yet been published.

Delayed Phase

The recommendations for prevention of delayed emesis following HE chemotherapy are not as clear cut as those for the acute phase. The incidence of delayed emesis in patients receiving cisplatin-based chemotherapy is reduced from 90% to 40-50% by the use of corticosteroids alone, or combined with metoclopramide or a 5-HT_3RA (IGAR, 1997; Kris et al., 1989; Latreille et al., 1998b; Navari, 2003). The 1999 American Society of Clinical Oncology (ASCO) and the American Society of Health-System Pharmacists (ASHP) guidelines recommended a combination of corticosteroid and either metoclopramide or 5-HT_3 RA for prevention of delayed emesis in patients receiving HE chemotherapy (ASHP, 1999; Gralla et al., 1999).

Early clinical trial results showed that the combination of dexamethasone and metoclopramide had higher antiemetic efficacy during the delayed phase as compared to dexamethasone alone (Kris et al., 1989). Several other studies have reported that the combination of a 5-HT_3RA and dexamethasone has similar efficacy as dexamethasone alone (Goedhals, Heron, Kleisbauer, Pagani, & Sessa, 1998; Latreille et al., 1998a; Tsukada, Hirose, Yokoyama, & Kurita, 2001). Thus based on the evidence, it can be concluded that the combination of dexamethasone and metoclopramide has better efficacy than dexamethasone alone and similar efficacy to dexamethasone and 5-HT_3 RA combination. Also, dexamethasone and 5-HT_3 RA combination does not provide any additional antiemetic benefit compared to dexamethasone alone.

The introduction of aprepitant led to the development of new guidelines and recommendations for prevention of delayed CINV following HE chemotherapy. The MASCC and NCCN recommends (MASCC, 2004; NCCN, 2005) using a combination of dexamethasone and aprepitant to prevent delayed emesis based on its superiority to dexamethasone alone (Hesketh et al., 2003; Poli-Bigelli et al., 2003). This combination has not been compared for its antiemetic efficacy to other combination regimens previously recommended. Since head-to-head clinical trials are not available, decision analytical models can be used to combine data from diverse sources to compare various antiemetic regimens to determine their cost-effectiveness (CE) compared to the new regimen. The dexamethasone and 5-HT_3RA combination needs to be studied as an alternative strategy for delayed emesis in the CE model due to its widespread use in clinical practice.

Moderately Emetogenic Chemotherapy

Acute Phase

A study was conducted among 428 patients receiving ME chemotherapy to compare three antiemetic regimens: dexamethasone alone, granisetron alone, and combination of dexamethasone and granisetron for prevention of acute emesis (IGAR, 1995a). The results showed that patients who received the combination regimen were found to have complete protection from both nausea and vomiting (70%) more frequently compared to patients receiving dexamethasone (49%) and granisetron (43%) alone. Thus, a combination of a 5-HT_3RA and dexamethasone was recommended by previous guidelines (ASHP, 1999; Gralla et al., 1999). The 2005 NCCN guidelines (NCCN, 2005) reiterate the recommendations of the previous guidelines and gives preference to palonosetron based on the results of the recent clinical trials (Eisenberg et al., 2003; R. Gralla et al., 2003).

Delayed Phase

In the absence of prophylactic antiemetic agents, the incidence of delayed emesis was 20-25% among patients receiving ME chemotherapy, such as cyclophosphamide plus either doxorubicin or epirubicin. But other studies have placed the incidence of delayed emesis in patients receiving ME chemotherapy without prophylactic antiemetic regimens as high as 70%. (IGAR, 2000b; Navari, 2003). Previous guidelines have recommended the use of either dexamethasone alone or combination of dexamethasone with a 5-HT_3RA or metoclopramide for prevention of delayed emesis due to ME chemotherapy (ASHP, 1999; Gralla et al., 1999). With the introduction of new antiemetic agents, aprepitant and palonosetron, new guidelines have been published. The 2005 NCCN and 2004 MASCC guidelines recommend either dexamethasone alone or a 5-HT_3 RA alone or combination of aprepitant and dexamethasone if aprepitant was given during the acute phase (MASCC, 2004; NCCN, 2005).

2.4: Economic Evaluation of Antiemetics for Prevention of CINV

The introduction of serotonin receptor antagonists in the early 1990's made a significant impact on the prophylaxis and management of CINV. Antiemetic regimens with 5-HT_3RAs have resulted in better antiemetic control in patients receiving HE and ME chemotherapy compared to the older antiemetic agents. But these agents are costly compared to the older antiemetic agents. The introduction of the new antiemetic agents, which provide better antiemetic control for

prevention of delayed emesis compared to only 5-HT_3RAs, has further increased the cost of prophylactic combination antiemetic regimens. Rising health care expenditure coupled with limited resources have led to an increased interest in conducting economic evaluations of healthcare interventions, a method in which both costs and benefits of interventions are evaluated to make resource allocation decisions. The next two sections outline some of the previous economic evaluations conducted to compare various antiemetic regimens for prevention of CINV following HE and ME chemotherapy.

A recent review of cost-effectiveness studies of antiemetics for CINV included 20 studies (Lachaine & Crott, 2003). Out of these 20 studies, 15 studies conducted cost-effectiveness analysis (CEA) comparing 5-HT_3RAs to traditional antiemetics such as metoclopramide and 5 studies compared 5-HT_3RAs against one another. A large number of these were limited to the acute phase of nausea and vomiting following administration of chemotherapy (Ballatori et al., 1994; Buxton & O'Brien, 1992; Cunningham et al., 1993; Sands et al., 1992).

For Highly Emetogenic Chemotherapy

A majority (14 studies) of the previous economic evaluations have been conducted for patients receiving HE chemotherapy. Ballatori and colleagues conducted a retrospective CEA using data from a study in cancer patients receiving cisplatin (Ballatori et al., 1994). The trial compared the antiemetic efficacy of an intravenous regimen of dexamethasone with either ondansetron or metoclopramide for prevention of acute emesis for three cycles of chemotherapy (IGAR, 1992). A hospital perspective was adopted for the study and the incremental cost-effectiveness ratio (ICER) was US$369 (1991 costs) for each additional patient with complete emesis control obtained by the ondansetron group. The impact of delayed emesis was not considered in the study. Also, the study was conducted based on multi-dosing regimens of antiemetics and studies since then have shown the equivalent efficacy of multi-dosing regimens to single-dose regimens of 5-HT_3RAs (Beck et al., 1992; Ettinger et al., 1996). Cost-effectiveness analysis based on single-dose regimens may lead to decreased personnel and drug administration costs and alter the ICER of the comparators. Thus, there is a need to conduct economic evaluations of new antiemetic regimens to the previous standard regimens using the optimal dosing regimens.

Economic evaluations comparing 5-HT_3RAs against one another have been conducted (Barrajon & de las, 2000; Becker et al., 1996). Two of those studies can be considered as cost minimization analyses since the efficacy of the comparators were considered to be equivalent and there were only cost differences (Barrajon & de las, 2000; Becker et al., 1996). Economic evaluations comparing 5-HT_3RAs to traditional antiemetics such as metoclopramide for prevention of acute CINV following HE chemotherapy showed that the higher costs of 5-HT_3RAs are compensated for by superior efficacy, less side effects and lower personnel and administration costs (Ballatori et al., 1994; Buxton & O'Brien, 1992; Cunningham et al., 1993; Sands et al., 1992). However, to our knowledge, none of the prior economic evaluations of antiemetics for prevention of CINV following highly emetogenic chemotherapy were conducted for delayed emesis or for the overall period of emesis.

Recently, three studies evaluating the cost-effectiveness of aprepitant given with standard regimen have been presented at international symposiums and published in abstract format (Deuson, 2004; Ehlken et al., 2004; Moore et al., 2005). Ehlken and colleagues conducted a CEA of adding aprepitant to the standard regimen of ondansetron and dexamethasone in patients undergoing highly emetogenic chemotherapy in office-based settings in Germany. The study was conducted from the payer's perspective. A decision analytic model was constructed to determine the costs and benefits associated with the two alternative strategies. The outcome measures were patients with complete control of emesis, i.e. no emesis and no rescue medications, and quality-adjusted life years (QALY). The effectiveness of the antiemetic regimens were obtained from phase III trials of aprepitant and the German tariffs and prices were used to value the health care resources associated with CINV. The results showed that 43% of the higher cost of aprepitant was offset by lower resource use. The incremental cost per QALY of aprepitant compared to the standard regimen was calculated to be €21,764. The results of sensitivity analyses showed that the results were sensitive to costs of hospitalizations and rescue medications. The authors concluded that the use of aprepitant in office-based settings in Germany was cost-effective.

Due to the inability to access the entire study, it is difficult to determine the source of utilities used in the estimation of QALYs. As discussed earlier, there is no consensus about the best method to generate utilities for short-term health states. The cost per QALY estimates obtained from the above study may be sensitive to the method used for utility elicitation. The

CEA in the study was based on the regimens used during the clinical trial, aprepitant and dexamethasone compared to dexamethasone alone for the delayed phase. But this does not reflect clinical practice where a combination of dexamethasone with a 5-HT_3RA is most commonly employed.

Another study was conducted to determine the cost-effectiveness of three regimens from the payer's perspective: standard therapy, adding aprepitant to the standard regimen (strategy 1) and adding aprepitant when CINV occurs (strategy 2) (Moore et al., 2005). The study used a Markov model to compare the two alternative strategies for a hypothetical cohort of patients receiving four cycles of HE chemotherapy. The outcomes measures used were healthy-days equivalent and QALYs. The probabilities and utilities for the model were obtained from the published clinical trials. The costs were based on resource use for CINV management using Medicare reimbursement rates for hospital and physician services and the average wholesale price (AWP) for medications. Compared to the standard regimen, the ICERs were $172,789/QALY for strategy 1 and $160,236/QALY for strategy 2. The probabilistic Monte Carlo trials showed that using the $50,000/QALY threshold, strategy 1 was not cost-effective in 89.7% of the trials. The authors concluded that aprepitant should be used after CINV occurs or should be used in high-risk populations for it to be cost effective.

For Moderately Emetogenic Chemotherapy

Several cost-effectiveness analyses of different antiemetic regimens for prevention of CINV due to ME chemotherapy have been conducted (Cox & Hirsch, 1993; Kwong & Parasuraman, 1999; Lachaine & Laurier, 2002; Lachaine, Laurier, Langleben, & Vaillant, 1999). Kwong and Parasuraman conducted a retrospective CEA of oral ondansetron and prochlorperazine for prevention of CINV in patients receiving ME chemotherapy. The outcome measure was defined as the number of patients who had no emetic episodes and no adverse events during the three day study period. The study was conducted from a third-party payer perspective. A decision analytic model was constructed to outline the outcomes of the treatment alternatives. The data on the probabilities of complete relief during the study period, of adverse effects, of requiring rescue medications, and hospitalizations were obtained from published clinical trials. The medication costs were based on the 1996 average wholesale price, and the hospitalization costs were based on expenses per inpatient day reported in the American Hospital Association's 1994 annual survey of hospitals. The incremental CEA showed that the cost of one

additional effectively treated patient with ondansetron was $258. The cost-effectiveness results were sensitive to variations in the duration of antiemetic therapy, total cost of antiemetic rescue medications and percentage of patients using ondansetron as rescue medication.

Recently, Vanscoy and colleagues conducted a pharmacoeconomic analysis of palonosetron in patients receiving ME chemotherapy from the payer perspective and concluded that palonosetron is a cost-effective treatment strategy compared to the older 5-HT_3RAs (Vanscoy et al., 2004).

2.5: Willingness-To-Pay (WTP)

Valuation of health gains produced by new interventions can be conducted by quality-adjusted life year (QALY) or willingness-to-pay (WTP) methodology. The QALY is a measure of health outcome which simultaneously captures improvement in HRQOL and gains in survival (Drummond, O'Brien, Stoddart, & Torrance, 1997). QALYs are calculated as the product of the change in utility value induced by the treatment and duration of the treatment effect. The utilities assigned to a specific state of health can be estimated using techniques such as Standard Gamble (SG), Time Trade-Off (TTO) or Rating Scale, or by means of pre-scored health state sorting systems (i.e. Health Utilities Index). The standard gamble (SG) method asks the respondent the probability of death that they are willing to accept to move from the diseased state to perfect health. The time trade-off (TTO) method requires the respondent to specify the number of years of life in perfect health that would be equivalent to the given number of years in the given health state.

CINV is an acute condition lasting for a period of 5-7 days. The impact of CINV on survival has not been established in clinical trials but it has a significant impact on morbidity which is reflected in HRQOL. The use of QALYs to value morbidity for short-term condition such as CINV has both measurement and evaluation problems (Bala & Zarkin, 2000). The measurement problems correspond to problems associated with eliciting the utility value for the health state in question in a valid and reliable fashion. In the SG method, the patients' preference for either maintaining a fixed intermediate health state or taking a gamble with perfect health and death as possible outcomes is determined. But for acute conditions like CINV, it is difficult for respondents to consider and evaluate the probability of immediate death that would be acceptable to them to move from a disease state that lasts for 5-7 days to perfect health. A study by Franic

and colleagues found that respondents were extremely risk averse with acute conditions such as CINV and the primary factor contributing to the refusal to gamble was the focus on death in the SG method (Franic & Pathak, 2003).

Two methods to overcome the problem of using death as a negative anchor for utility elicitation for CINV-related health states is to use the cascading or chained SG method or chained TTO method (Furlong, Feeney, & Torrance, 1990; Jansen, Kievit, Nooij, & Stiggelbout, 2001; Jansen et al., 1998). In these methods, a surrogate negative anchor health state is used instead of death. The surrogate negative anchor is a health state severe enough for the patient to be able to visualize this state in relation to the gamble of perfect health and immediate death. The other health states are then evaluated in comparison with perfect health vs. surrogate negative anchor state. The scores thus obtained are then adjusted in proportion to the utility of the surrogate negative anchor health state which has been determined using the traditional utility elicitation methods (Grunberg, Srivastava, Grunberg, & Weeks, 2002; Jansen et al., 1998). One of the drawbacks of this approach is that patients who are presented with an anchor health state find it irrelevant to the situation of interest. The results of chained TTO or SG methods may also be affected by the anchor state used in the chaining procedure (Bala & Zarkin, 2000).

In addition to measurement problems, the use of QALYs for acute health conditions has evaluation issues which correspond to problems in using the elicited health utility value to make optimal health care coverage decisions. Zbrozek et al. (1995) performed a cost utility analysis comparing ondansetron with metoclopramide using efficacy data from published clinical trials. To calculate the incremental cost per QALY, a relative difference of 0.00014 QALY between two antiemetic agents was arbitrarily estimated. The incremental cost per QALY in patients receiving high-dose cisplatin was US$407,667 and in patients receiving moderate-dose cisplatin was US$372,255. One of the reasons for such a high incremental cost-effectiveness ratio (ICER) is that the multiplicative product of the utility weights and life-years gained, which in the case of CINV is small due to the acute nature of the health condition, leads to high cost per QALY estimates. Thus, an alternative technique to valuing health benefits produced by new interventions is the WTP methodology.

Monetary Valuation of Health Outcomes

The WTP methodology directly estimates the value of health gains in monetary terms which can be then used to conduct cost-benefit analysis (CBA). CBA is a method of economic evaluation in which health benefits are valued in monetary terms. There are three methods to the monetary valuation of health outcomes or benefits: a) human capital approach, b) revealed preferences and c) contingent valuation (CV) (Drummond et al., 1997). The human capital approach is not recommended to measure health outcomes in monetary terms since it is production-based and is not consistent with the principles of welfare economics. The revealed preference method is an indirect measurement method, which has been used in wage-risk trade off studies (Gafni, 1991). These studies are undertaken to understand the association between health risk associated with particular jobs and the wages that individuals require to accept the job. Though this method is based on actual consumer behavior, it is context and job-specific and cannot be applied widely (Drummond et al., 1997).

The contingent valuation (CV) method is based on stated preferences where the respondents are asked to value goods in a contingent or hypothetical market using survey measures (O'Brien & Gafni, 1996). Contingent valuation involves direct measurement in which respondents are asked to provide either their maximum WTP to maintain the current level of utility or minimum willingness to accept (WTA) to make the utility equal to what it would have been after the change. WTP is a method to determine the monetary value that patients place on health improvements, for example, improved emetic control. WTP estimates for improved emetic control can provide important evidence to managed care and hospital formulary committees to justify budgetary increases for new antiemetic agents such as aprepitant and palonosetron. The individual can be assumed to take into account all the attributes of the commodity while considering their maximum WTP.

2.6: Methodological Issues in WTP

Willingness-to-pay using the CV method is based on the premise that the maximum amount of money an individual is willing to pay for a commodity is an indicator of the utility or satisfaction to them of that commodity. In implementing the CV method to determine WTP for improved emesis control, the following methodological issues need discussion: global versus restricted measurement of benefits, perspective of analysis (ex-ante and ex-post user), payment

vehicle (out-of-pocket, or increases in insurance premiums or increases in tax payments), and format of the WTP question (single open-ended, or multiple close-ended questions) (O'Brien & Viramontes, 1994; Smith, Olsen, & Harris, 1999a)

Global vs. restricted approach

The three broad categories of benefits that arise from any health care program include: 1) intangible benefits which are the value of the improved health to the consumer of the program, for example: prevention of nausea and vomiting, impact of intervention on improving HRQOL; 2) future health care costs avoided, for example: cost of breakthrough emesis, additional physician visits, hospitalization, any cost to patient and/or health care sector associated with suboptimal control of emesis; 3) increased productive output due to improved health status, for example: work productivity.

In the restricted approach to WTP, the respondents are asked to value only the intangible health benefits for which market values do not exist. The future health care savings and increased productive outputs are valued using market prices (Drummond et al., 1997). One of the problems with the restricted approach is development of valuation scenarios that can isolate the health effects of the intervention from other effects such as out-of-pocket costs, income lost due to time off work etc. (Currie et al., 2002). On the other hand, the global approach to WTP asks the respondents to take into account all the potential benefits of the commodity while considering their maximum WTP. While using the global approach to assessing WTP, respondents should be told explicitly to consider income effects due to work absence due to disease (emesis) or its treatment (side effects of antiemetics), cost offsets due to improved emesis control etc. Depending upon the complexity and amount of information presented, there may be substantial cognitive burden placed on the study respondents.

Perspective of the WTP analysis

WTP can be measured using either the ex-post/user-based perspective or the ex-ante/insurance-based perspective. In the ex-post or user-based approach, respondents know that they are consumers of the treatment, i.e. either patients who already have the disease in question (cancer and receiving chemotherapy) or individuals presented with hypothetical scenarios with a certainty of having the disease in question and only the treatment outcomes are uncertain (probability of complete control of emesis). This method captures only the user values since the

valuation involves certain use of the program and only uncertainty in the outcomes of the health program. Respondents for WTP surveys based on user perspective can include patients or caregivers, random sample of general population and convenient samples. General population and convenient samples are provided with scenarios where they are asked to assume to have the disease in question and state their WTP for uncertain health outcomes.

In the ex-ante perspective, along with the uncertain treatment outcomes, the valuation needs to incorporate the probability of contracting the disease and needing the service in question in the future. Thus, in this perspective the respondents are provided with the probabilities of being diagnosed with cancer in the future, requiring chemotherapy and complete control of emesis due to the antiemetic interventions. WTP surveys with ex-ante perspective are conducted in random samples of the general population or convenient samples to include currently diseased individuals, currently non-diseased who are at future risk of disease, and currently non-diseased who are not themselves at personal risk of the disease. The respondents are asked their WTP as increase in insurance premiums to ensure coverage for the health intervention for a specified disease. In countries with national health care system funded by tax monies, respondents are asked their WTP as increase in tax payment amounts over their lifetime.

It is thought that the WTP questions in the context of health care should be framed in the form of hypothetical insurance purchasing since users typically do not pay for medical services at the point of consumption and due to its ability to capture user, option and externalities values (Gafni, 1991). But respondents may have difficulty understanding the multiple uncertainties involved in the hypothetical scenario for determining WTP for improved emesis control based on ex-ante perspective. These could include: incidence of cancer in a specified period of time, probability of receiving HE or ME chemotherapy, probability of emesis with chemotherapy and uncertainty associated with antiemetic regimen outcomes. These compound probabilities can pose substantial cognitive burden for the respondents. It can also be argued that the patients who are experiencing the condition are the best candidates to provide the value of the benefits provided by the related health interventions. Thus, for the purpose of this study, we will use the user-based perspective for determination of WTP.

Payment vehicle (Out-of-pocket, tax, insurance)

The most common payment vehicles are direct out-of-pocket (OOP) payments, additional tax payments, and private insurance premiums. The user-based perspective usually employs

OOP payments whereas; the ex-ante perspective employs additional tax payments or increase in insurance premiums as payment vehicle (Smith, Olsen, & Harris, 1999b). There is a lack of consensus regarding the appropriate payment vehicle. Some argue (Birch, 1993) that insurance premiums should be used whereas others argue (Donaldson et al, 1995) for different vehicles (Smith et al., 1999b). It is likely that appropriateness of payment vehicle for a particular commodity will depend on the type of product, and different health care systems. For example, insurance premiums may be appropriate for the USA but not for the United Kingdom where increased taxation would be more appropriate. Similarly, insurance premiums may be the appropriate vehicle for high technology items or expensive low probability items and OOP in the form of increased co-payments for pharmaceuticals (Drummond et al, 1997). Smith, Olsen and Harris (1999) (Smith et al., 1999b) recommend that OOP payment is most relevant if users are asked, whereas taxation is most relevant if the general population is asked in ex-ante perspective. For the purpose of our study, OOP payments will be the payment vehicle, as it is an appropriate approach for WTP for pharmaceuticals using user-based perspective. We will not ask WTP as OOP payments in increased co-payments since respondents may base their responses on their current co-payment structure.

Questionnaire format/Survey method

The WTP questions can be presented in five formats: 1) open-ended; 2) bidding game; 3) payment card; 4) discrete-choice and 5) discrete choice with follow-up (Smith, 2000).

1) Open-ended questions

The respondents are simply asked to report their maximum willingness-to-pay. This format may produce unbiased estimates of WTP since the respondents are not prompted. Though easy to construct, open-ended questions are too hypothetical, do not reflect the way people behave in the market and may be cognitively challenging for respondents, as they are not used to answering such questions (Donaldson, Shackley, & Abdalla, 1997). The WTP estimates may be imprecise due to wide variance and many non-responses or protest responses (Johannesson, 1996).

2) Bidding game method

In the bidding game method, the respondents are provided with an initial WTP amount, which they can either accept or reject. Depending on whether they accept or reject the amount, a higher or lower bid, respectively is presented and the process is continued until the maximum WTP is reached. The bidding game method has improved precision but it may introduce a

starting point bias, in which the respondents' answers may be biased by the initial amounts presented in the bidding game. There is no consistency in the published health care literature about the presence of starting point bias in the bidding game method of eliciting WTP. Health care studies specifically conducted to test for starting point bias did not show evidence of its presence (O'Brien & Viramontes, 1994; O'Brien et al., 1998).

3) Payment card method

Payment cards have a specified range of values and the respondents are asked to indicate which amounts they will definitely not pay, which amounts they will definitely pay and what is the maximum amount they would pay for the health intervention. The payment card approach was developed by Mitchell and Carson (Mitchell & Carson, 1981) and is believed to simulate real-life situations by allowing the individuals to "shop around" for a value that they would most pay (Donaldson, Thomas, & Torgerson, 1997). Donaldson and colleagues (Donaldson et al., 1997) showed that compared to the open-ended format, the payment card method yields higher response rates to WTP questions, more consistent mean and median values, and a stronger association between WTP and ability to pay.

The payment card method may be susceptible to range bias i.e. the range of amounts presented may influence the WTP responses (Neumann & Johannesson, 1994; Ryan, Scott, & Donaldson, 2004). Midpoint or centering bias may also be a potential bias in WTP estimates using payment card method. Midpoint bias is said to occur when the respondents have a tendency to state the midpoint of the range as their WTP (Ryan, 2004). Studies have shown conflicting results about the presence of range and centering bias with Neumann and colleagues (1994) reporting its presence whereas a study by Ryan and colleagues (2004) did not find significant range or centering bias in their study. Another study conducted to test for range and centering bias used four versions of payment card with different ranges and center values and did not find the existence of these biases (Rowe, Schulze, & Brefle, 1996).

4) Discrete choice (DC) method

The DC method also referred to as the referendum method is the recommended format by the US National Oceanic and Atmospheric Administration Panel on contingent evaluation (NOAA) (National Oceanic and Atmostpheric Administration, 1993). Each respondent is provided with a single WTP amount, which they either accept or reject. Thus, each respondent provides limited information about his or her WTP, which may be either equal, or above or below the presented amounts. Different bids are presented to different subsamples, and then

statistical methods are used to determine the societal WTP. The DC method can be modified by introducing single bid-up or double bid-up following the initial amount. In the single bid-up method, based on the acceptance or rejection of the initial WTP amount, the respondent is provided with a higher or a lower bid amount. In the double bid-up method, the iterations are truncated after providing two follow-up bids. Though the DC method avoids starting point and range bias, the single-bid up and double-up versions of the method are susceptible to these biases. This is because the single bid-up amount and the double bid-up amounts will be based on the starting value used in the method. Also, the DC method is highly inefficient as large sample size is required to identify the distribution of values with a degree of accuracy.

2.7: Willingness-To-Pay (WTP) Studies in CINV Literature

To date, only one study measuring the monetary value of improved emesis control has been published. Following phase II randomized clinical trials establishing efficacy of NK-1 receptor antagonists, Dranitsaris et al (2001) undertook a multinational study (countries included were Canada, Italy, Greece and Spain) to measure the maximum amount that cancer patients would be willing to pay for reducing their risk of CINV following cisplatin-based chemotherapy. Willingness-to-pay for various scenarios of absolute risk reduction of acute and delayed emesis was assessed using the CV approach and the user-based perspective. The respondents were presented with background information on CINV and the current treatments for emesis followed by the various clinical scenarios for eliciting WTP. A payment card method was used to avoid starting point bias and the first value given by the respondent was recorded as the WTP estimate. Sociodemographic information such as age, marital status, education, family income, religious affiliation and clinical characteristics such as diagnosis, history of previous chemotherapy, previous emesis and treatment location were collected.

Results showed that cancer patients from Canada, Italy and Spain were willing to pay $US46, $US34, and $US63 per day compared to $US8 for patients from Greece for 20% risk reduction in acute emesis (baseline risk was 30%). For 30% risk reduction in delayed emesis (baseline risk was 40%), Canadian, Italian and Spanish cancer patients were willing to pay $US41, $US31, and $US50 daily for four days compared to US$9 for Greek patients. Multivariate analyses adjusting for sociodemographic variables and previous history of emesis showed that significant differences in patient value between countries still remained. For acute and delayed emesis, family income was the only other significant variable predicting maximum

WTP. The results also bring to light the cultural or geographical differences in the mean WTP for improved control of emesis.

WTP for improved emesis control due to the addition of aprepitant to the standard regimen for prevention of CINV due to highly emetogenic chemotherapy and use of palonosetron instead of the other 5-HT_3RA for prevention of CINV due to ME chemotherapy has not been conducted in the United States. The NK-1 receptor antagonist, aprepitant is recommended for a period of 3 days whereas the study provided a scenario with hypothetical antiemetic benefit and duration of regimen.

To our knowledge, there are no studies that have conducted comprehensive economic evaluation of the new antiemetic regimens for prevention of CINV following HE and ME chemotherapy. No study has evaluated the cost-effectiveness of an antiemetic regimen with aprepitant compared to the standard regimen of 5-HT_3RA and dexamethasone, and regimen recommended by ASCO and clinical practice. Lastly, due to the acute nature of CINV, a cost-benefit analysis using monetary value of improved emetic control would be appropriate for resource allocation decisions. The next chapter provides the objectives for the two phases of the study and outlines the detailed methodology employed in order to achieve the study objectives.

CHAPTER THREE

METHODOLOGY

The study was conducted in two phases. Phase I involved constructing two decision analytic models to determine the incremental costs and benefits of alternative antiemetic regimens for prevention of chemotherapy-induced nausea and vomiting (CINV) following 1) highly emetogenic (HE) and 2) moderately emetogenic (ME) chemotherapy. Phase II involved conducting face to face interviews to determine the maximum amount that patients with cancer were willing to pay for improved emesis control provided by new antiemetic regimens. The monetary value of the benefits of the new antiemetic regimens were used in cost-benefit analyses (CBA) to estimate the net benefits provided by the new regimens.

3.1: Phase I - Development of Decision Analytical Model

It is expensive and time consuming to conduct clinical trials to compare an intervention to all its relevant alternatives. In spite of that, the critical data obtained from clinical trials along with other evidence is required to optimize the use of healthcare interventions. Thus, there is a tradeoff between obtaining evidence of effects of alternative healthcare interventions and the cost of obtaining such evidence. Decision models represent the sequence of chance events and decisions over time. These models are one of the ways to synthesize evidence from different sources in an attempt to form decisions about optimal health care interventions (Mandelblatt et al., 1996).

Two decision analytical models were constructed to identify the relevant costs and consequences of alternative antiemetic regimens for prevention of CINV following administration of HE and ME chemotherapy. For the purpose of this study, HE chemotherapy includes only cisplatin-based chemotherapy, which causes acute emesis in 99% of cancer patients receiving it. The ME chemotherapy includes agents, which results in acute emesis in 30-90% of patients and are listed in Table 2-3.

The cost-effectiveness analyses (CEA) were conducted from two different perspectives, namely societal and third-party payer. The use of multiple perspectives is to make the study

results relevant to different groups of stakeholders. The societal perspective is the broadest perspective and includes the costs and benefits of the health care intervention, irrespective of who incurs it. The CEA conducted from societal perspective includes both direct and indirect costs associated with the intervention. It is also the recommended approach for CEA by the Panel on Cost-effectiveness in Health and Medicine, U.S. Public Health Service (Gold, Siegel, Russell, & Weinstein, 1996). CEA conducted from the societal perspective also helps in decision making for allocation of resources from a public policy framework. Conducting CEA from the societal perspective does not preclude us from conducting analyses from other perspectives of interest to specific groups. Groups such as hospitals and payers are interested in making decisions about coverage of effective but costly health care interventions by taking into account the costs and benefits that are relevant to their setting. Thus, CEA conducted from the narrower third-party payer perspective will assist the relevant groups in formulary decision-making for alternative antiemetic regimens. The CEA conducted from the payer's perspective include only the direct costs related to the intervention incurred by the payer.

Intervention and Alternative Strategies

The rationale for choosing the alternatives for the decision models were explained in Chapter 1. The choice of the antiemetic intervention strategies was based on recommendations following the introduction of new antiemetic agents, regimens employed in clinical trials of the new antiemetics, previous guidelines and commonly used regimens in clinical practice.

Alternative Strategies for Prevention of CINV Following HE Chemotherapy

Table 3-1 describes the prophylactic antiemetic strategies in terms of dosage, formulations and duration of therapy for prevention of CINV following administration of HE chemotherapy.

Table 3-1: Antiemetic Strategies for Prevention of Chemotherapy-Induced Nausea and Vomiting following Highly Emetogenic Chemotherapy

Strategies	Acute Phase (Day 1)	Delayed Phase (Days 2-4)
Regimen A (Aprepitant)	Oral Aprepitant 125 mg Oral Dexamethasone 12 mg IV Ondansetron 32 mg	Oral Aprepitant 80 mg (Days 2-3) Oral Dexamethasone 8 mg (Days 2-4)
Regimen B (Only dexamethasone)	Oral Dexamethasone 20 mg IV Ondansetron 32 mg	Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C (Metoclopramide combination)	IV Dexamethasone 20 mg IV Ondansetron 8 mg	IM Dexamethasone 8 mg BID (Days 2-3) and 4 mg BID (Day 4) Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D (Ondansetron combination)	IV Dexamethasone 20 mg IV Ondansetron 8 mg	IM Dexamethasone 8 mg BID (Days 2-3) and 4mg BID (Day 4) Oral Ondansetron 8 mg BID (Days 2-4)

Addition of aprepitant to the standard regimen, regimen A in Table 3-1, has been recommended by the Multinational Association of Supportive Cancer Care (MASCC) as the regimen of choice for prevention of acute and delayed emesis following cisplatin-based HE chemotherapy (MASCC, 2004). Regimen B has been employed as the comparator antiemetic strategy in clinical trials of aprepitant (Hesketh et al., 2003; Poli-Bigelli et al., 2003). The other comparators, regimens C and D are based on previous guidelines published by the American Society of Clinical Oncology (ASCO), which recommended the use of combination therapy of dexamethasone with either metoclopramide or a 5-HT_3RA for prevention of delayed emesis (Gralla et al., 1999).

The combination therapy of dexamethasone and a 5-HT_3RA has been extensively used in clinical practice for management of delayed emesis (DURTO, 2003), even though there is not sufficient evidence to suggest that it has higher efficacy as compared to the dexamethasone and metoclopramide combination. Thus, it is important to compare the two combination strategies for prevention of delayed emesis since metoclopramide, in large doses is associated with side effects in large doses whereas 5-HT_3RAs are more expensive compared to metoclopramide. Thus, based on published guidelines and clinical practice, we will compare the MASCC recommended regimen to the standard regimen used in clinical trials, the regimen recommended by ASCO, and a widely used regimen in clinical practice.

Alternative Strategies for Prevention of CINV Following ME Chemotherapy

Table 3-2 describes the prophylactic antiemetic strategies in terms of dosages, formulations and duration of therapy for prevention of CINV following administration of ME chemotherapy. Regimen 1 is IV administration of a single dose of palonosetron before chemotherapy and regimen 2 is a single IV dose of an older 5-HT_3RA which has been employed as the comparator in clinical trials of palonosetron. The NCCN recommendations include a 5-HT_3RA and dexamethasone combination for prevention of acute emesis due to ME chemotherapy and either dexamethasone or a 5-HT_3RA for prevention of delayed emesis. The antiemetic strategy regimen 3 reflects the NCCN 2005 guidelines. The 1999 ASCO guidelines recommend a combination of a 5-HT_3RA and dexamethasone for prevention of delayed emesis and this is included as regimen 4 in the model.

Randomized controlled clinical trials have shown that the older 5-HT_3RAs (ondansetron, dolasetron and granisetron) are equivalent in their efficacy, and their oral dosage forms are also

equivalent to their intravenous forms. A majority of the randomized clinical trials conducted for establishing the efficacy of aprepitant and palonosetron have used ondansetron as the comparator. Thus, for the purpose of this study, ondansetron will be representative of the 5-HT_3 RA class of drugs.

Table 3-2: Antiemetic Strategies for Prevention of Chemotherapy-Induced Nausea and Vomiting following Moderately Emetogenic Chemotherapy

Strategies	Acute Phase (Day 1)	Delayed Phase (Days 2-5)
Regimen 1 (Only Palonosetron)	IV Palonosetron 0.25 mg	-
Regimen 2	IV Ondansetron 32 mg	-
Regimen 3 (2005 NCCN)	IV Ondansetron 8 mg IV Dexamethasone 8 mg	Oral Dexamethasone 8mg BID (Days 2-5)
Regimen 4 (1999 ASCO)	IV Ondansetron 8 mg IV Dexamethasone 8 mg	Oral Dexamethasone 8mg BID (Days 2-5) Oral Ondansetron 8mg BID (Days 2-5)

Model Structure and Simulation

The decision analytical models for antiemetic regimens for prevention of CINV following HE and ME chemotherapy for a single cycle are described in Figure 3-1. The models were developed using TreeAge Pro software (TreeAge Software, Inc., 2005). The first branch point on the decision tree is a decision node indicating a choice of prophylactic antiemetic regimens for prevention of CINV. Subsequently, the decision model is identical for all the treatment alternatives. After receiving chemotherapy and a prophylactic regimen for the acute phase, patients can either experience acute emesis or no acute emesis.

No Acute Emesis Arm:

For patients who do not experience acute emesis, these patients may or may not receive rescue medications for control of nausea in the acute phase. In both cases, patients could experience delayed emesis or no delayed emesis. The incidence of delayed emesis is assumed to be dependent on the prophylactic antiemetic regimen received in the acute phase and the CINV control obtained in the acute phase. The control of delayed CINV is assumed to be independent of the receipt of rescue medications in the acute phase. Patients who do not experience any delayed emesis may or may not receive rescue medications to control for delayed nausea. Following this, patients may or may not experience the side effects due to the antiemetic regimens. For the base-case analysis of both decision models, it was assumed that the proportion of adverse events is the same for all the alternative antiemetic regimens. If patients experience delayed emesis they may or may not receive rescue medications. In both instances, patients could either receive outpatient care for uncontrolled emesis or may not require further care.

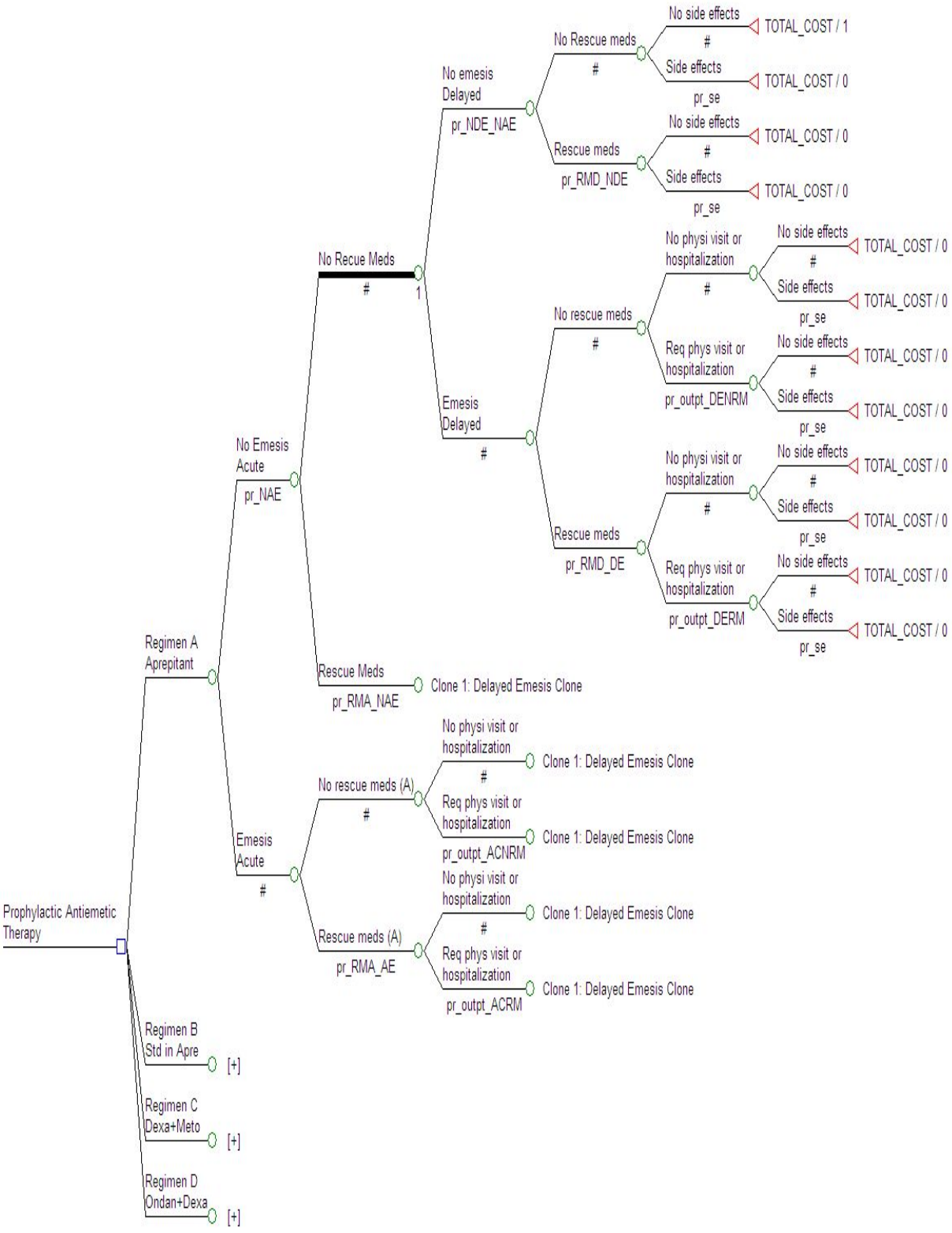
Acute Emesis Arm:

For patients who do experience acute emesis, they can either receive or not receive rescue medications. Subsequently, these patients may or may not require outpatient care for uncontrolled emesis. Following this, patients may or may not experience delayed emesis and subsequently, the model is identical to those who had no acute emesis.

Most clinical studies conducted to determine the efficacy of antiemetic agents for prevention of CINV following HE chemotherapy pertain to cisplatin-naïve adult patients receiving their first cycle of single day cisplatin-based HE chemotherapy. Therefore, a hypothetical cohort of 10,000 cisplatin-naïve cancer patients over the age of 18 who are

scheduled to receive their first cycle of single day, outpatient, cisplatin-based chemotherapy regimen was considered for the HE decision analytical model. Based on the mean age of the population in the aprepitant clinical trials the mean age of the hypothetical cohort was assumed to be 55 years. Similarly for the ME decision model the hypothetical cohort was chosen such that its underlying characteristics were similar to the population in the clinical trials conducted for determining the efficacy of antiemetic agents following ME chemotherapy. Therefore, for the ME decision model, a hypothetical cohort of 10,000 chemotherapy-naïve patients over the age of 18 who are scheduled to receive their first cycle of single day, outpatient, ME chemotherapy such as, any dose of carboplatin, epirubcin, cyclophosphamide < 1,500mg/m^2, doxorubicin > 25 mg/m^2, or cisplatin <50 mg/m^2 was considered. The mean age of the cohort was 55 years.

Figure 3-1: Structure of the Decision Analytical Model for Determining Cost-Effectiveness of Prophylactic Antiemetic Regimens



Time Horizon of Analysis

Chemotherapy is usually administered to cancer patients for four to six cycles. Economic evaluation of antiemetic regimens for prevention of CINV should be conducted for multiple cycles of chemotherapy to capture all the relevant costs and benefits. Thus, ideally, the model should represent four to six cycles of chemotherapy to capture the costs and outcomes comprehensively. However, randomized controlled clinical trials for multiple cycles of chemotherapy have only been conducted for the new regimen and the standard antiemetic regimen. Due to lack of clinical efficacy data for multiple cycles for the other alternatives, the decision analytical model was constructed to represent only one cycle of chemotherapy. The time horizon of the model was five days to coincide with the actual time for which patients experience CINV during one cycle of chemotherapy.

For both HE and ME chemotherapy models, the primary outcome measures are the cost per completely controlled patient at the end of the five-day period. Completely controlled is defined as no episodes of emesis and no use of rescue medications in both acute and delayed phases. For the societal perspective, the total costs included the direct costs associated with prevention and treatment of CINV and indirect costs due to lost work productivity due to uncontrolled CINV. The CEA conducted from the third-party payer's perspective included only the direct costs associated with prevention and treatment of CINV.

Data for the Decision Models

The following section describes in detail data that were used to populate the model. The probabilities of various events and associated treatment costs were the two types of data required to populate the models. Probabilities of various events in the decision models can be obtained through direct observation, review of the published literature or expert opinion. A comprehensive review of the literature was conducted to get relevant probabilities of various events in the decision model. For probabilities not available from published literature, expert opinion was used. The expert opinion was obtained by conducting structured interviews with a panel of oncologists and oncology nurses.

Probabilities for HE Decision Model

Efficacy of Alternative Prophylactic Regimens

The efficacy data represents the probability of achieving complete control of acute and delayed emesis following the administration of the four prophylactic antiemetic regimens. The base case estimates for acute and delayed efficacy of the alternative regimens are shown in Table 3-3. The table also includes the ranges of estimates that were used to conduct sensitivity analyses.

The efficacy data for regimens A and B were based on the published results of two multi-center, randomized, double blind placebo controlled phase III trials (Hesketh et al., 2003; Poli-Bigelli et al., 2003). In both trials, patients were randomized to receive either the standard regimen or the three-drug combination containing aprepitant. The studies were conducted in cisplatin-naïve patients above 18 years of age who were scheduled to receive their first cycle of chemotherapy including $\geq 50mg/m^2$ of cisplatin. The studies were used to determine the probability of no acute emesis, no delayed emesis among those with no acute emesis and no delayed emesis among those with acute emesis. Since the distribution of the study population based on demographic characteristics was different for the two studies, the averages of the probabilities obtained were used as base case estimates. For conducting sensitivity analyses, the higher of the two estimates obtained from the two studies was used as the upper limit of the range for the probability of no acute emesis. The lower limit of the range was set at the efficacy of the standard regimen (74.2%) which includes the lower estimate obtained from the clinical trials and also enable us to determine the robustness of the results if the benefit of the aprepitant regimen is same as the standard regimen in the acute phase. The ranges for probabilities of no delayed emesis given no acute emesis and no delayed emesis given acute emesis were based on the individual estimates obtained from the two clinical trials.

The antiemetic drugs used for prophylaxis of acute emesis are same in regimens C and D. The efficacy of the regimen for control of acute emesis was obtained from three randomized controlled clinical trials (IGAR, 1995b, 1997, 1998a) and one observational study (IGAR, 2000a). The base case estimate of no acute emesis for regimens C and D was estimated to be 79.9%, calculated as the average of the individual estimates obtained from the four studies. Similar to the range for regimen A, the upper limit was the highest estimate obtained from the studies and the lower limit was set to be equal to the base case estimate of regimen B.

The efficacy of regimen C in controlling delayed emesis was based on the published results of two studies, one observational study and one multi-center, randomized double-blind trial (IGAR, 1997, 2000a). The proportion of patients who do not have delayed emesis given that they have control of acute emesis was calculated to be 73.55% and given that they have acute emesis was 14.40%. The efficacy of regimen D in controlling delayed emesis was based on a randomized, double blind trial conducted by the Italian Group for Antiemetic Research (IGAR, 1997).

Receiving Rescue Medications for Breakthrough Emesis

The base case probabilities for receiving rescue medications for breakthrough emesis and the ranges used for sensitivity analyses are presented in Table 3-4. For regimens A and B, the probability of receiving rescue medications following no acute emesis, acute emesis, no delayed emesis and delayed emesis were obtained from calculations conducted using published data from two randomized clinical trials of aprepitant (Hesketh et al., 2003; Poli-Bigelli et al., 2003). In these two clinical trials, rescue medications were given for any degree of nausea or vomiting due to chemotherapy. The receipt of rescue medications in the delayed phase was assumed to be dependent on the prophylactic antiemetic regimen received for the delayed phase. The receipt of rescue medications was assumed to be independent of the level of control of acute emesis or on the receipt of rescue medications in the acute phase.

The clinical trials conducted to study the efficacy of regimens C and D (IGAR, 1995b, 1997, 1998a) stipulated the use of rescue medications only for patients with three or more episodes of emesis whereas, the protocol of clinical trials for aprepitant and the standard regimen stipulated that patients with any degree of nausea or vomiting could receive rescue medications (Hesketh et al., 2003; Poli-Bigelli et al., 2003). Thus, for regimens C and D, the probability of receiving rescue medications in the acute phase following no acute emesis and acute emesis is assumed to be equal to that for regimen B. This assumption was made since the antiemetic drugs for the acute phase are the same for the three regimens except for the difference in the dose of ondansetron. The difference in the dose of ondansetron will not have an impact on the incidence of emesis or use of rescue mediation since studies have shown that IV 8 mg offers similar acute antiemetic efficacy as compared to IV 32 mg. In a randomized, double-blind clinical trial conducted to determine the efficacy of regimens C and D for delayed emesis, rescue medications were given for patients experiencing three or more emetic episodes in the delayed phase (IGAR

1997). Due to lack of relevant and appropriate information in the included clinical trials, the average of the corresponding estimates for regimens A and B were used.

For those who experience acute or delayed emesis, the probability of receiving rescue medications was ranged from the lower limits obtained from the individual study estimates and the higher limits were set at 100%, i.e. all patients in the cohort who experience emesis will receive rescue medications. The lower limit of the range for sensitivity analyses for the parameters: probability of receiving rescue medications given no acute emesis and no delayed emesis were set at zero and the higher limit was set at the higher of the estimates obtained from the included studies.

Table 3-3: Base-Case Estimates and Sensitivity Analysis Ranges of Efficacy of Prophylactic Antiemetic Regimens for Acute and Delayed Phase – For HE Model

Parameter	Baseline Estimate	Lower limit	Upper limit	References
No Acute Emesis				
Regimen A	0.870	0.742	0.900	1, 2
Regimen B	0.742	0.690	0.793	1, 2
Regimen C	0.799	0.742	0.832	3, 4, 5, 6
Regimen D	0.799	0.742	0.832	3, 4, 5, 6
No Delayed Emesis Given No Acute Emesis				
Regimen A	0.830	0.793	0.866	1, 2
Regimen B	0.670	0.646	0.694	1, 2
Regimen C	0.736	0.733	0.738	4, 5
Regimen D	0.715	0.572	0.858	5
No Delayed Emesis Given Acute Emesis				
Regimen A	0.317	0.308	0.326	1, 2
Regimen B	0.154	0.122	0.185	1, 2
Regimen C	0.144	0.088	0.200	4, 5
Regimen D	0.286	0.228	0.343	5

References: 1. (P. J. Hesketh et al., 2003); 2. (Poli-Bigelli et al., 2003); 3. (IGAR, 1995b); 4. (IGAR, 2000a)
5. (IGAR, 1997); 6. (IGAR, 1998a)

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 3-4: Base-Case Estimates and Sensitivity Analysis Ranges for Receiving Rescue Medications for Uncontrolled CINV – For HE Model

Parameter	Baseline Estimate	Lower limit	Upper limit	References
In the acute phase given no acute emesis				
Regimen A	0.012	0.000	0.015	1, 2
Regimen B	0.012	0.000	0.015	1, 2
Regimen C	0.012	0.000	0.015	Assumed*
Regimen D	0.012	0.000	0.015	Assumed*
In the acute phase given acute emesis				
Regimen A	0.338	0.175	1.000	1, 2
Regimen B	0.394	0.304	1.000	1, 2
Regimen C	0.394	0.304	1.000	Assumed*
Regimen D	0.394	0.304	1.000	Assumed*
In the delayed phase given no delayed emesis				
Regimen A	0.050	0.000	0.055	1, 2
Regimen B	0.028	0.000	0.035	1, 2
Regimen C	0.039	0.000	0.045	Assumed**
Regimen D	0.039	0.000	0.045	Assumed**
In the delayed phase given delayed emesis				
Regimen A	0.576	0.454	1.000	1, 2
Regimen B	0.531	0.477	1.000	1, 2
Regimen C	0.553	0.465	1.000	Assumed**
Regimen D	0.553	0.465	1.000	Assumed**

* Assumed based on the estimates for Regimen B as the acute phase antiemetics are same for the two regimens
** Assumed to be the average of estimates of regimen A and B.
References: 1. (P. J. Hesketh et al., 2003); 2. (Poli-Bigelli et al., 2003)

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)

Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Adverse Events due to Prophylactic Antiemetic Regimens

For the base-case model, it was assumed that the probability of experiencing adverse events is similar between the four regimens. The probability of adverse effects due to regimen C was modeled to conduct a scenario analysis. Thus for scenario analysis, only the adverse events due to metoclopramide for regimen C were modeled and the adverse events due to the other three regimens were assumed to be similar. The serious adverse reactions associated with the use of metoclopramide are parkinsonism and/or other extrapyramidal reactions. These consist often of a feeling of restlessness, facial spasms, involuntary movements and in some cases, muscular twitching. Schnell and colleagues reported that five percent of patients receiving metoclopramide will experience extrapyramidal symptoms (EPS) (Schnell, 2003). Based on their database, Bleiberg and colleagues reported that 2.6% of patients had EPS due to metoclopramide (Bleiberg, Autier, & Michaux, 1994). The average of the two estimates was used as the probability of experiencing EPS in patients receiving regimen C. Extrapyramidal reactions have been successfully controlled by antiparkinson and antihistamine/anticholinergic agents such as 25-50 mg of diphenhydramine hydrochloride. It was assumed that all patients experiencing EPS will require treatment with diphenhydramine hydrochloride.

Probability of Outpatient Physician Visit due to Uncontrolled Emesis

The probability of uncontrolled emesis resulting in an outpatient physician visit or inpatient hospitalization is very low. But since it involves a substantial amount of healthcare resource utilization, the costs need to be modeled to provide an accurate representation of management of CINV. The probability of requiring an outpatient visit for receiving intravenous saline infusion and rescue medications was based on a structured interview conducted among an expert panel consisting of three oncologists and three oncology nurses. The survey used for the interview is included as Appendix I. Based on the responses obtained from the survey, the probability of outpatient visits in the acute phase is extremely rare and 0.01 was used as the base case probability. For sensitivity analysis, the probability was ranged from zero to 3% based on the survey responses. Ihbe-Heffinger and colleagues (Ihbe-Heffinger et al., 2004) conducted a study among German cancer centers and reported that 2.5% were hospitalized for dehydration due to uncontrolled severe nausea and vomiting. Our survey respondents reported that approximately 5% of patients may require additional care due to severe nausea and vomiting in the delayed phase. Based on these estimates, the baseline probability of requiring outpatient

physician visit for uncontrolled delayed emesis was estimated to be 3.5% and was ranged from 2%-5% for sensitivity analyses.

Probabilities for ME Decision Model

Efficacy of Alternative Prophylactic Regimens

The efficacy data represents the probability of achieving complete control of acute and delayed emesis following administration of the four prophylactic antiemetic regimens. The base case estimates for acute and delayed efficacy of the alternative regimens are shown in Table 3-5. The table also includes the ranges that were used to conduct sensitivity analyses.

The efficacy data for regimens 1 and 2 were based on the published results of a multi-center, randomized, double blind, phase III trial conducted to study the antiemetic efficacy of palonosetron in patients receiving moderately emetogenic chemotherapy (Gralla et al., 2003). In this clinical trial, patients were randomized to receive either the standard regimen of a single IV dose of ondansetron 32 mg or a single IV dose of palonosetron 0.25 mg. The study results were used to determine the probabilities of no acute emesis, no delayed emesis among those with no acute emesis, and no delayed emesis among those with acute emesis. The ranges for sensitivity analysis of probabilities of no acute emesis and no delayed emesis among those with no acute emesis were set at ±20% of the baseline probability estimates. If the probability exceeds 1.00, the upper limit was reduced. The sensitivity analysis range for the probability of no delayed emesis among those with acute emesis was ranged from 0.0 to 0.30. The upper limit of 0.30 was chosen to test the robustness of the results if the probability was as high as the base case estimate of regimen 3.

Table 3-5: Base-Case Estimates and Sensitvity Analysis Ranges of Efficacy of Prophylactic Antiemetic Regimens for Acute and Delayed Phase – For ME Model

Parameter	Baseline Estimate	Lower limit	Upper limit	References
No Acute Emesis				
Regimen 1	0.850	0.680	0.900	1
Regimen 2	0.720	0.576	0.864	1
Regimen 3	0.892	0.714	0.900	2, 3, 4, 5
Regimen 4	0.892	0.714	0.900	2, 3, 4, 5
No Delayed Emesis Given No Acute Emesis				
Regimen 1	0.924	0.739	0.950	1
Regimen 2	0.812	0.649	0.950	1
Regimen 3	0.855	0.684	0.950	2, 4
Regimen 4	0.952	0.762	1.000	2
No Delayed Emesis Given Acute Emesis				
Regimen 1	0.133	0.000	0.300	1
Regimen 2	0.107	0.000	0.300	1
Regimen 3	0.300	0.000	0.568	2, 4
Regimen 4	0.568	0.300	0.682	2

References: 1. (R. Gralla et al., 2003); 2. (IGAR, 2004); 3. (Kaizer et al., 1994); 4. (IGAR, 2000c); 5. (Warr et al., 2005)

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

The antiemetic drugs used for prophylaxis of acute emesis are the same in regimens 3 and 4. The IGAR conducted a dexamethasone dose-finding study among patients receiving moderately emetogenic chemotherapy (IGAR, 2004). One of the study arms employed a combination of 8mg IV ondansetron and 8 mg IV dexamethasone as the prophylactic acute antiemetic regimen. The results for this study arm were used as the baseline estimates for the probability of no acute emesis for regimens 3 and 4. The range for sensitivity analyses were set at ±20% of the baseline probability estimates. This range included the individual estimates obtained from the results of three randomized controlled clinical trials that employ the same regimen with different dosing schedules (IGAR, 2000c; Kaizer et al., 1994; Warr et al., 2005)

The efficacy of regimen 3 in controlling delayed emesis was based on the published results of two randomized clinical trials (IGAR, 2000c, 2004). The results obtained from one study arm of a randomized clinical trial (IGAR, 2004) were used as baseline estimates for the probability of no delayed emesis given no acute emesis and probability of no delayed emesis given acute emesis for regimen 3. The range for sensitivity analysis was set at ±20% of the baseline probability estimates, which included the individual estimates obtained from the two studies for the probability of no delayed emesis given no acute emesis. For the probability of no delayed emesis given acute emesis the lower limit was set at 0.00 and the baseline estimate of regimen 4 was set as the upper limit. This range included the individual estimates obtained from the two randomized clinical trials. The efficacy of regimen 4 in controlling delayed emesis was based on a randomized, double blind trial conducted by the Italian Group for Antiemetic Research (IGAR, 2000c). The range for the sensitivity analyses was set at ± 20% of the baseline estimates.

Receiving Rescue Medications for Breakthrough Emesis

The base case probabilities for receiving rescue medications for breakthrough emesis and the ranges used for sensitivity analyses for the ME model are presented in Table 3-6.

Table 3-6: Base-Case Estimates and Sensitivity Analyses Ranges for Receiving Rescue Medications for Uncontrolled CINV – For ME Model

Parameter	Baseline Estimate	Lower limit	Upper limit	References
In the acute phase given no acute emesis				
Regimen 1	0.047	0.000	0.104	1
Regimen 2	0.047	0.000	0.104	1
Regimen 3	0.104	0.000	0.125	2
Regimen 4	0.104	0.000	0.125	2
In the acute phase given acute emesis				
Regimen 1	0.300	0.240	1.000	Assumed
Regimen 2	0.300	0.240	1.000	Assumed
Regimen 3	0.523	0.300	1.000	2
Regimen 4	0.523	0.300	1.000	2
In the delayed phase given no delayed emesis				
Regimen 1	0.074	0.000	0.100	1
Regimen 2	0.097	0.000	0.120	1
Regimen 3	0.085	0.000	0.120	Assumed*
Regimen 4	0.085	0.000	0.120	Assumed*
In the delayed phase given delayed emesis				
Regimen 1	0.500	0.400	1.000	1
Regimen 2	0.472	0.378	1.000	1
Regimen 3	0.486	0.389	1.000	Assumed*
Regimen 4	0.486	0.389	1.000	Assumed*

* Assumed to be the average of estimates of regimen 1 and 2. **References**: 1. (R. Gralla et al., 2003); 2. (Warr et al., 2005)
Regimen 1: IV Palonosetron 0.25mg; **Regimen 2**: IV Ondansetron 32mg; **Regimen 3**: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5); **Regimen 4**: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

For regimens 1 and 2, the probability of receiving rescue medications following no acute emesis, no delayed emesis, and delayed emesis were obtained from calculations conducted using published data from a randomized clinical trial of palonosetron (Gralla et al., 2003). The receipt of rescue medications following acute emesis was assumed to be 0.30 for regimens 1 and 2.

For regimens 3 and 4, the probability of receiving rescue medications in the acute phase following no acute emesis and following acute emesis, was assumed to be equal because it was the same acute phase antiemetic regimen. This probability was obtained from a randomized controlled trial (Warr et al., 2005). Due to lack of relevant data in the published literature, the average of the probability estimates of regimens 1 and 2 were used as baseline estimates for receiving rescue medications in the delayed phase following no delayed emesis and delayed emesis.

For those patients who experience acute or delayed emesis, the probability of receiving rescue medications was ranged from the lower limits calculated as -20% of baseline and the upper limits were set at 1.00, i.e. all patients in the cohort who experience emesis will receive rescue meds. The lower limit of the range for sensitivity analyses for the parameters: probability of receiving rescue medications given no acute emesis and no delayed emesis were set at zero and the higher limit was set at +20% of the baseline estimates.

Adverse Events due to Prophylactic Antiemetic Regimens

The $5HT_3$RAs including palonosetron have been found to have a favorable side effect profile as compared to some of the older antiemetic agents such as metoclopramide. A randomized double-blind controlled clinical trial conducted to determine the efficacy and safety of palonosetron compared to ondansetron, found no significant differences in the proportion of treatment-related adverse events in the two groups (Gralla et al., 2003). The prophylactic antiemetic regimens used for prevention of CINV in the ME model were comprised of similar individual antiemetics and thus it was assumed that the probability of experiencing adverse events is similar between the four regimens. Thus, adverse events were not modeled for the ME model.

Probability of Outpatient Physician Visit due to Uncontrolled Emesis

The probability of uncontrolled emesis resulting in an outpatient physician visit or inpatient hospitalization is very low. However, because it involves a substantial amount of healthcare resource utilization, the costs need to be modeled to provide an accurate representation of management of CINV. There is no reason to believe that the probability of outpatient physician visits due to uncontrolled emesis will be dependent on the type of chemotherapy received. The probability is more likely to depend only on the level of uncontrolled emesis experienced by the patients. Thus, for this study, it is assumed that the probability of receiving outpatient physician visits is similar to those for the HE model and also similar for all treatment strategies.

Cost Estimates for the Decision Models

Direct Costs

The direct costs for the model included the costs of prophylactic antiemetic regimens, drug administration, rescue medications for managing breakthrough emesis, outpatient care for uncontrolled emesis and treating adverse events of antiemetic regimens.

Costs of Prophylactic Antiemetic Regimens

The drug costs for prophylactic antiemetic regimens, rescue medications and medications to treat side effects were obtained from the Drug Topics Red Book (Red Book, 2005). The Red Book lists the average wholesale price (AWP) for virtually every medicine prescribed. For drugs which are available in generic forms, the average of the highest and lowest prices was used as the drug cost. The unit costs for the various antiemetic agents and rescue medications are provided in Table 3-7.

Table 3-7: Unit Costs for Individual Antiemetic Drugs Used in the Decision Models

Drug	Base case cost	Upper limit	Lower Limit
Prophylactic Antiemetic Drugs			
Aprepitant 125 mg	$108.77	$87.02	$130.52
Aprepitant 80 mg	$100.12	$80.10	$120.14
IV Ondansetron 32 mg	$206.41	$165.13	$247.69
IV Ondansetron 8 mg	$51.28	$41.02	$61.54
Oral Ondansetron 8 mg	$36.72	$29.38	$44.06
IV Dexamethasone 20 mg	$4.04	$1.31	$6.60
Oral Dexamethasone 4 mg	$1.57	$0.67	$2.33
IM/IV Dexamethasone 8 mg	$4.15	$1.34	$4.66
Oral Metoclopramide 20 mg	$1.43	$0.55	$3.22
IV Palonosetron 0.25mg	$340.20	$272.16	$408.24
Rescue Medications			
Oral Prochlorperazine 10 mg	$0.82	$0.58	$1.07
Oral Promethazine 25 mg	$0.52	$0.45	$0.59
Oral Lorazepam 1mg	$1.01	$0.57	$1.32

For antiemetic drugs that were administered as infusion, administration costs were added to the treatment costs. The administration costs were based on the G codes published by Medicare for reimbursement (Department of Health and Human Services, 2004). The reimbursement values for drug administration are appropriate for CEA conducted from the payer's perspective but not for the societal perspective. For the societal perspective, the actual costs incurred for administering the antiemetic drugs should be used for the analysis. However, in most cases the actual costs are not publicly available and the reimbursed charges are most commonly employed. Thus, the Medicare reimbursement values have been used in this study for CEA conducted from the societal perspective. The base case value is ranged between ± 20% to conduct sensitivity analyses. The cost of prophylactic antiemetic regimens, administration costs and the total treatment costs for the various strategies are shown in Tables 3-8 and 3-9.

Table 3-8: Cost of Prophylactic Antiemetic Regimens Used in the Decision Analysis Model - For HE Model

Costs	Regimen A	Regimen B	Regimen C	Regimen D
Prophylactic antiemetic drugs	$530.00 (±20%)	$233.10 (±20%)	$93.23 (±20%)	$296.39(±20%)
Administration	$58.95 (±20%)	$58.95 (±20%)	$86.67 (±20%)	$86.67 (±20%)
Total Regimen	$588.50 (±20%)	$292.05 (±20%)	$179.90 (±20%)	$383.06 (±20%)

Table 3-9: Cost of Prophylactic Antiemetic Regimens Used in the Decision Analysis Model - For ME Model

Costs	Regimen 1	Regimen 2	Regimen 3	Regimen 4
Prophylactic antiemetic drugs	$340.20 (±20%)	$206.41 (±20%)	$67.99 (±20%)	$361.75 (±20%)
Administration	$58.95 (±20%)	$58.95 (±20%)	$86.67 (±20%)	$86.67 (±20%)
Total Regimen	$399.15 (±20%)	$265.36 (±20%)	$154.66 (±20%)	$448.42 (±20%)

Costs of Managing Breakthrough Emesis

The rescue medications prescribed for breakthrough emesis were based on the 2005 NCCN guidelines. In previous economic evaluations it was assumed that patients will experience on average two emetic episodes during a 24-hour time period and thus two doses of rescue medications will be provided each day (Johnson & Bosanquet, 1995; Kwong & Parasuraman, 1999). The base case analysis in this study was conducted assuming that patients are prescribed prochlorperazine (Compazine) twice a day for one day for breakthrough emesis during the acute phase and four times a day for two days during the delayed phase. The costs and benefits were calculated for two scenarios where the drugs used for managing breakthrough emesis in delayed phase were changed to a 5-HT_3RA for regimens B and C. This is because the prophylactic regimen for delayed phase does not include a 5-HT_3RA and it may be preferred instead of prochlorperazine for managing breakthrough emesis.

Based on unstructured interviews with oncology nurses at the cancer center it was found that nurses conduct follow-up phone calls with patients to inquire about side effects of chemotherapy. It was assumed that all patients who received rescue medications during the delayed phase would spend a minimum of 15 minutes on the phone with the nurse to relate CINV events. The hourly wage rate for registered nurses was multiplied with the time taken on the phone to calculate the personnel costs associated with managing breakthrough emesis. The costs for managing breakthrough emesis are presented in Table 3-10.

For patients that require additional care for extreme CINV event, it was assumed that the patient will come for an outpatient visit and will require intravenous infusion of saline and rescue antiemetic medications. It was assumed that the probability of requiring additional outpatient care does not differ based on the prophylactic antiemetic regimen received.

Indirect Costs Associated with Management of CINV

Indirect costs associated with CINV were included to capture the impact of potential savings associated with control of CINV with each treatment. O'Brien and colleagues (O'Brien et al., 1993) conducted a study in five Canadian cancer centers to determine the costs associated with CINV. The study reported a total loss of 198 hours of paid employment, 409 hours of unpaid employment, and 186 hours of caregiver time among 72 patients who experienced emesis.

Based on this study, we assumed that the patient's average time away from paid or unpaid work was 11.00 hours (the total of time away from employment – 793 divided by 72 patients). The time away from work due to uncontrolled CINV was valued using the adult average wage rate obtained from the Bureau of Labor Statistics (US Department of Labor, 2005). The base case estimate was varied between 2.75 hours (estimated using only loss of paid employment) and 24 hours (3 days) of lost employment for conducting sensitivity analyses.

For the CEA conducted from the payer perspective, direct total cost included the cost of the total regimen, cost associated with managing breakthrough emesis, cost of outpatient care for uncontrolled emesis and cost of treating adverse events of antiemetic agents. The indirect costs were added to the direct total costs for CEA conducted from the societal perspective.

Table 3-10: Costs of Managing Breakthrough Emesis

Resources	Unit Costs	Upper Limit	Lower Limit
Rescue Medications			
Oral Prochlorperazine 10 mg	$0.82	$0.58	$1.07
Total Personnel costs (For delayed phase)			
Average Salary – Registered Nurse	$26.61/hour	$21.29/hour	$31.93/hour
Total Cost of Outpatient Visit			
Saline Infusion 1000cc	$0.99	$0.79	$1.19
Physician Outpatient Visit	$48.98	$39.18	$58.78
Administration cost for saline (1^{st} hr)	$64.8	$51.84	$77.76
Administration cost for saline (2^{nd} hr)	$41.38	$33.10	$49.66

Model Assumptions and Rationale

1. In clinical practice, agents such as lorazepam, prochlorperazine or promethazine are prescribed in combination with the prophylactic antiemetic regimens included in the decision models for prevention of CINV. It was assumed that the effectiveness, toxicity and cost of these additional drugs will be consistent across the alternative treatment strategies and thus have not been included in the model.

2. Lindley and colleagues have reported the level of compliance with three-single drug antiemetic regimens in patients receiving moderately high to highly emetogenic chemotherapy (Lindley et al., 2005). The study results showed no significant differences in the level of compliance among patients receiving prochlorperazine (83%), dexamethasone (85%) and ondansetron (80%). Currently, there is a lack of information on the level of compliance with combination antiemetic regimens and whether it differs based on the type of chemotherapy received by the patients. For this study, it was assumed that patients have 100% compliance with the antiemetic regimens in the acute and delayed phase. Thus, any incidence of emesis in the acute or delayed phase was not due to non-compliance but a result of lack of efficacy by the prophylactic antiemetic regimen.

3. The incidence of delayed emesis is known to be dependent on the level of control in the acute emesis and the prophylactic antiemetic regimens prescribed (IGAR, 1994; Schnell, 2003). The incidence of delayed emesis was assumed to be independent of the receipt of rescue medications or additional outpatient care in the acute phase. The receipt of rescue medications or outpatient care in the delayed phase is assumed to be dependent only on the incidence of emesis in the delayed phase and independent of the type of prophylactic antiemetic regimen received. The probability of receipt of rescue medications and outpatient care for each regimen is varied in sensitivity analyses to test the robustness of the study results.

4. Ideally, failures (patients who experience emesis/nausea/emesis and nausea) should be assessed by the average number of emetic episodes per patient per treatment. Since all clinical trials do not provide the average number of emetic episodes experienced per patient explicitly, it is assumed that patients experience two emetic episodes on average in each 24 hours. It was also assumed that two doses of rescue medications will be required in 24 hours

for all the treatment arms (Johnson & Bosanquet, 1995; Kwong & Parasuraman, 1999). For uncontrolled delayed emesis, it was assumed that patients receive rescue medications for two days. The estimates of number of doses of rescue medication and number of days were varied in sensitivity analyses to test the robustness of the CEA results.

5. It was assumed that patients will either receive or not receive rescue medications for control of emesis or nausea and were assumed to have achieved control of emesis/nausea/both emesis and nausea if subsequent outpatient care is not required.

6. Only costs due to lost productivity during the delayed phase were included in the model as the indirect costs. The workday lost during the acute phase is not included in the indirect cost estimates as it is incurred by all patients irrespective of the treatment received.

7. The costs incurred by patients in hiring additional help for child care, home care or caregiver costs were not included in the model. The out-of-pocket costs for managing nausea and vomiting which may include cleaning costs, laundering soiled clothes were not included in the model. These costs will be based on the number of emetic episodes experienced by the patients and in our model, this was assumed to be similar for all treatment strategies. Thus, increasing the costs by the same amounts in all the treatment arms would not affect the ICER calculations.

8. Patients may use over the counter medications for treating nausea and vomiting and it is assumed that the usage will be similar in all the treatment arms. Since the costs and benefits associated with these medications are assumed to be the same in all arms, their inclusion will not affect the ICER calculations and are not included in the model.

9. For the HE model, only the side effects due to metoclopramide were modeled. It was assumed that the adverse events in the other regimens due to the individual antiemetics will be similar. Thus incorporating the costs for treating adverse events by the same amounts in all the treatment arms will not affect the ICER calculations.

Base-case Cost Effectiveness Analysis

Decision models can be evaluated using either cohort simulation or first-order simulation model. In the first-order Monte Carlo simulation, a large number of patients are followed

through the model individually. A single patient is randomly selected and will randomly select a path at each change node in the decision model based on the probability of each outcome. The path followed by different patients will differ based on chance. Due to the process being repeated for a large number of times, first-order Monte Carlo simulation models can be used to estimate the sample mean and standard deviation associated with the costs and effects in each arm of the model.

The base case analysis represents the average costs and effectiveness for a hypothetical cohort of 10,000 patients. The baseline model was analyzed using a first-order Monte Carlo simulation and this helps in determining the uncertainty associated with the derived costs and outcomes. The average costs and effectiveness obtained were then used to calculate the incremental cost-effectiveness ratio (ICER) for each treatment strategy. The ICER for a treatment strategy is calculated as the additional cost per completely controlled patient relative to the next most costly option. These analyses were performed for both HE and ME models from the payer and the societal perspective.

Sensitivity Analyses

Sensitivity analysis is a means of assessing the extent to which the incremental costs and incremental effectiveness of the alternative regimens are affected by parameter uncertainty and model assumptions (Briggs, Sculpher, & Buxton, 1994). There are multiple methods which can be used to conduct sensitivity analysis: one-way, two-way, multi-way, threshold analysis and probabilistic sensitivity analyses (Briggs et al., 1994). In this study, one way sensitivity analyses were conducted, in which each critical study parameter was varied over a plausible range to evaluate key assumptions and test the robustness of the model.

Although, one-way sensitivity analyses are easy to understand, incremental costs and effectiveness do not depend on single parameters. Probabilistic sensitivity analysis is a method by which all parameters can be varied simultaneously to understand the overall impact on incremental costs and effectiveness (Agro et al., 1997; Briggs, Goeree, Blackhouse, & O'Brien, 2002). Probabilistic sensitivity analysis (second-order Monte Carlo simulation) was conducted to assess the impact of simultaneous variations in the distribution of important variables around their point estimates. In second-order Monte Carlo simulation each parameter with a specified range is associated with a distribution function and repeated samples are drawn at random from these distributions to determine empirical distribution of cost-effectiveness ratio for each

treatment strategy (Shaw & Zachry, 2002). The simulation can be run to generate hundreds of scenarios of different combinations of input variables and generate the output values for a strategy. Probabilistic sensitivity analysis provides superior information since it uses distributions of input values instead of just a single mean value.

3.2: Phase II: Willingness-to-Pay and Cost-Benefit Analyses

The objectives of phase II are 2.1) to determine the monetary value placed on improved emesis control due to addition of aprepitant to the standard regimen following administration of HE chemotherapy using WTP method, 2.2) to determine the monetary value placed on improved emesis control with the introduction of palonosetron instead of the standard regimen following administration of ME chemotherapy using WTP method, 2.3) to determine the association between maximum WTP for improved emesis control following HE chemotherapy and respondents' demographic and clinical characteristics, 2.4) to determine the association between maximum WTP for improved emesis control following ME chemotherapy and respondents' demographic and clinical characteristics, 2.5) to determine the net benefit of addition of aprepitant to the standard antiemetic regimen for prevention of CINV due to HE chemotherapy and 2.6) to determine the net benefit of palonosetron as the antiemetic drug for prevention of CINV due to ME chemotherapy. In order to achieve the Phase II objectives, primary data will be collected using a survey. The study population, survey instrument, data collection process and the statistical techniques for Phase II are described below.

WTP Elicitation Using Contingent Valuation (CV) Method

WTP is based on the premise that the maximum amount of money an individual is willing to pay for a commodity is an indicator of the utility or satisfaction to them of that commodity. The contingent valuation (CV) method was used to assess consumers' WTP for a program. It is a direct measurement of WTP using a survey-based approach to elicit monetary (in this case, dollar) values by presenting hypothetical scenarios about the healthcare intervention under evaluation. The following section describes the methodology employed for measuring patients' WTP for 1) improved emesis control due to addition of aprepitant (new drug) to the antiemetic regimen ($5HT_3$ RA + dexamethasone) following HE chemotherapy – Scenario 1 and 2) improved emesis control due to the new drug palonosetron compared to the antiemetic regimen ($5HT_3$ RA + dexamethasone) following ME chemotherapy – Scenario 2. The main

purpose of determining the WTP is to use the monetary valuation of benefits of antiemetic regimen for conducting CBA of the emerging antiemetic regimens for preventing CINV following HE and ME chemotherapy from a payer perspective.

The CV method was used to value the benefits offered by the two antiemetic agents. For the purpose of this study, WTP was determined from the ex-post/user-based perspective. The multiple uncertainties and use of compound probabilities involved in the ex-ante perspective can pose a substantial cognitive burden for the respondents. Also, patients who are experiencing the condition are considered to be the best candidates to provide the value of benefits provided by the health interventions. For the purpose of this study, out-of-pocket payment was chosen as the payment vehicle, as it is an appropriate approach for estimating WTP for pharmaceuticals using the user-based perspective. A payment card format was employed to determine the maximum WTP for improved emesis control for the two scenarios, HE chemotherapy and ME chemotherapy. WTP can be asked in the various formats (explained in chapter 2) but each method is susceptible to a number of potential biases. Range bias in payment scale format has been assessed but it was not found to be a significant factor (Ryan et al., 2004). Since the payment card method provides a format where the consumer can "shop around" for a value that they would most likely pay which is close to a realistic scenario, it was the format of choice in this study.

Study Population, Sample selection and Sample Size Estimation

Study Population

Population is an aggregation of study elements. In most cases, it is practically impossible to survey the entire population. The survey sample is a subset of the population that is used to gain information about the entire population. For the user-based perspective, the survey sample can be drawn either from cancer patients or from the general population who are provided with hypothetical scenarios where respondents are asked to assume that they have cancer.

The population for Phase II of this study was cancer patients recruited from the Mary Babb Randolph Cancer Center (MBRCC) in Morgantown, WV. Patient preferences may be preferred when an analysis is designed to evaluate alternative interventions for the same condition and is not primarily intended for resource allocation decisions over a wide range of illness. A patient population is appropriate for this study, since the purpose of our study is to

assess the most efficient way to create health given a defined condition, i.e. CINV and a selection of treatment choices, i.e. antiemetic regimens.

Sample Selection

Patients with cancer who were 18 years or older in age and receiving their first or subsequent cycle of chemotherapy, or who have received chemotherapy in the past three months in an outpatient setting were eligible to participate in the study. Eligible participants should be able to understand and speak English. Also, based on the discretion of the oncologist or the oncology nurses, patients with cognitive impairment were excluded from the study.

Sample Size Estimation

The sample size for the study was based on the number of patients required to detect a minimum mean difference in willingness to pay of $30 for both the scenarios. The population standard deviation required for sample size calculation was obtained from a pilot study conducted among 20 patients. The details of the pilot study are discussed later. The sample size required for the study was determined using the PASS 6.0 software. By accepting $\alpha = 0.05$ (i.e., the probability of type I error is 5%), $\beta = 0.15$ (i.e., 85% detection power), standard deviation = $100.00, and a minimum difference in maximum WTP between the alternative regimens for Scenario 1 and Scenario 2 = $30, the estimated sample size required for the study would be 100 patients.

Recruitment Procedures and Data Collection

Approval for the survey instrument and the script for recruitment of participants were sought from the Institutional Review Board of West Virginia University. The oncologist or the oncology nurse approached eligible participants and explained the purpose of the study. The primary researcher described the study in detail and verbal consent was obtained, if patients were interested in participating in the study. The script for approaching and recruitment of patients for the study is attached as Appendix II.

Data collection can be done by face-to-face interviews, self-administered surveys, mail surveys or telephone interviews. In this study, data were collected by conducting face-to-face interviews with the patients when they come to the cancer center for regular check-ups, or for receiving chemotherapy. There is agreement in the literature that face-to-face interviewing is the

most preferred and reliable method for WTP elicitation (National Oceanic and Atmostpheric Administration, 1993);(Mitchell & Carson, 1989). Face-to-face interviewing allows for presenting the maximum amount of information, provides an opportunity for respondents to consider their response and for reducing the potential for hypothetical bias (Smith et al, 1999b; (Olsen & Smith, 2001). On completion of the interview, the participants were presented with a West Virginia University souvenir mug as a token of appreciation for their time and effort. Data was collected over a period of four months from mid-January to mid-May, 2005.

WTP Instrument Development

The WTP survey was developed by obtaining information from the published literature and a multidisciplinary team of oncologists, a clinical pharmacist, health services researchers and a health economist. Two versions of the survey were used, differing only in the order of presentation of the two hypothetical scenarios. In Version A, the HE chemotherapy scenario was presented first, followed by the ME chemotherapy scenario, whereas in Version B, the order was reversed. Participants were alternately assigned to the two versions of the survey. The survey has five sections and is presented as Appendix III. The global approach was used to construct the scenarios for WTP elicitation.

The first section of the survey attempted to standardize the knowledge base of participants by presenting information on chemotherapy, description of nausea and vomiting, risk of emesis following chemotherapy, and standard treatment used to prevent emesis. Section two of the survey was designed to collect information about clinical characteristics, such as type of cancer, prior experience with chemotherapy, prior experience of nausea and vomiting due to chemotherapy, severity of nausea experienced and number of emetic episodes during acute and delayed phases.

Patients were told at the beginning of the session that the scenarios presented were hypothetical and did not relate to their own personal situation. Sections three and four of the survey include the description of the two clinical scenarios and all the relevant information about the antiemetic regimens. The two scenarios differ in the type of chemotherapy received by the patients, and prophylactic antiemetic regimens compared. The actual names of the new drugs or the standard treatment were not used for scenario descriptions. In scenario 1, patients were asked to imagine that they are receiving HE chemotherapy which causes acute emesis in greater than

99% of patients and delayed emesis in greater than 75% of patients. This was followed by the description of the standard antiemetic regimen and the new regimen (standard regimen with aprepitant) for prevention of CINV following HE chemotherapy. In Scenario 2, patients were asked to imagine that they are receiving ME chemotherapy which causes acute emesis in 30-90% of patients and delayed emesis in 55% of patients. This was followed by the description of the standard antiemetic regimen and the new regimen (palonosetron) for prevention of CINV following ME chemotherapy.

After information about each scenario was presented, respondents were asked whether they prefer the new regimen compared to the standard regimen for each scenario and the reasons for their preferred choice. This was followed by eliciting information about how important they considered the acute and delayed risk reduction due to the new regimens on a scale of 0 to 10, where 0 is not at all important and 10 is very important. Respondents were asked to imagine that the new antiemetic regimens will not be covered by their drug insurance plans. They were asked to indicate the maximum amount that they would be willing to pay out-of-pocket for improved emesis control (reduction in acute emesis from 30% to 17% and delayed emesis from 55% to 37%) due to addition of a three-day regimen of aprepitant to the standard regimen in scenario 1. Similarly, respondents were asked to indicate the maximum amount that they would be WTP out of pocket for improved emesis control (reduction in delayed emesis from 45% to 33%) for a single day treatment with palonosetron instead of the standard regimen. The maximum WTP was determined using the payment card method. The payment card had a range of WTP amounts that were obtained by conducting a pilot survey of the instrument in 20 patients.

Many people are not willing to forgo any money for health gains because either they are opposed to paying for health or they oppose the suggestion of paying out of pocket or increase in taxes or insurance premiums. The protest is typically expressed as zero responses but sometimes may be excessively high amounts. For respondents who provided $0 as the maximum WTP, it is important to determine whether it is “genuine” valuation of the benefits of the intervention or a “protest” zero. A follow-up question was asked to respondents who provided $0 as WTP to determine if it was a protest zero or a genuine zero. Respondents were also asked to record the level of difficulty they had in understanding the hypothetical scenarios and to provide a maximum WTP amount. The time taken to complete the interview was also recorded.

Section 5, the last section of the survey was designed to obtain demographic information such as age, gender, education, marital status, employment status, number of members in the household, annual income before taxes, and insurance status.

Instrument Validation

Questionnaire Validity

The survey was reviewed by a multidisciplinary team of an oncologist, a clinical pharmacist and health outcomes researchers to assess its content validity. The qualitative feedback obtained from the team regarding the relevance of questions, clarity of questions and response options were was used to modify the survey. Based on the feedback, the efficacies of the regimens described in the hypothetical scenarios were presented using pie charts. The modified survey was then used to conduct a pilot study. The construct validity of the final survey was assessed by testing the positive relationship between income levels and WTP amounts, which is discussed in the data analysis section.

Pilot Study

A pilot study was used to determine the range for the payment card method and to establish the time taken to complete the survey. The other goals of the pilot study were to assess the respondents' level of understanding of the scenarios and WTP questions. The study was conducted among 20 cancer patients who were receiving chemotherapy or had received in the past three months. In the pilot study, the patients were presented with open-ended question to elicit their maximum WTP for the improved emesis control due to the new antiemetic regimen. A range for the payment card for the final survey was created from the responses of the pilot survey.

Data Handling and Data Analysis

The principal investigator was responsible for obtaining, organizing, analyzing and maintaining the data. The first two objectives (2.1 and 2.2) of Phase II of the study are to determine the maximum amount that patients with cancer are WTP for improved emesis control for both scenarios. The actual amount marked on the payment card range was considered as the maximum WTP amount. Summary WTP is usually presented as the mean and/or median. Though, the mean is sensitive to the shape of the distribution and less robust than the median, it is theoretically the correct measure of benefits for conducting a CBA. It is recommended that

mean WTP along with the range of values should be presented as a summary welfare measure in WTP studies (Smith, Olsen, & Harris, 1999c). In this study, WTP estimates for scenario 1 and scenario 2 have been presented as means and medians. The average WTP estimates for the entire sample, sample excluding all zeroes and sample excluding only the protest zeroes are reported. Demographic and clinical characteristics of the sample are presented as means, medians or proportions. Appropriate statistical tests were conducted to determine the differences in mean WTP amount based on demographic and clinical characteristics.

Objectives 2.3 and 2.4 involve determining the association between WTP for improved emetic control and patients' demographic and clinical characteristics for both scenarios. Based on the manner in which the WTP data is treated, different regression models can be employed to study the association between WTP and respondent characteristics. Some researchers consider the WTP data obtained from payment card method as censored data and the use of OLS models for censored dependent variable violates the assumption that the error term is normally distributed (Cameron & Huppert, 1989; Donaldson, Jones, Mapp, & Olsen, 1998). To overcome the problems with OLS models, researchers have explored the use of grouped data regression models to determine association of WTP with respondent characteristics (Donaldson et al., 1998). Another method is to consider the maximum WTP amount indicated on the payment scale as a continuous variable and use it as a dependent variable for ordinary least squares (OLS) regression models.

Usually, studies employing payment card for WTP elicitation instructs the respondent to circle an amount in the range provided that is closet to their maximum WTP amount. In this case, the maximum WTP amounts are restricted by the ranges provided and grouped regression models should be used for analyses. However, in this study, the respondents were instructed to specify the exact WTP amount if the amount they wish to circle was not shown in the payment card range. Thus, the maximum WTP amounts are not restricted by the limited range provided and can be considered as continuous variable and OLS models can be used to determine the association of WTP and respondent characteristics. A number of studies employing payment card method have used OLS regression model for the purpose of determining the association between WTP and annual household income level (Davey et al., 1998; Dranitsaris, 1997; Dranitsaris et al., 2001a; O'Brien, Novosel, Torrance, & Streiner, 1995). Also, in practice, OLS may provide a robust estimator of the mean WTP (Donaldson et al., 1998).

If the observed WTP amount indicated on the payment scale has a skewed distribution, regression analyses with logarithmic of WTP as dependent variable will be performed. Multivariable regression models were performed for the sample with positive WTP values. All statistical analyses were conducted in SPSS Version 13.0.

Cost-Benefit Analyses of Antiemetic Regimens

The last two objectives (2.5 and 2.6) of Phase II involve conducting CBA for determining the net benefit of using the new regimens instead of the standard regimens for prevention of CINV following HE and ME chemotherapy. The CBA were conducted from the payer perspective.

Calculation of Net Benefit

Cost benefit analysis is an economic evaluation method where the costs and benefits of the health care intervention are valued in monetary terms. The analytic time period of the CBA model is one chemotherapy cycle and a payer perspective will be undertaken. WTP amounts were used as monetary measures of improved emesis control, i.e. incremental benefits of the new antiemetic regimens over the standard regimens for prevention of CINV following HE and ME chemotherapy. The cost parameters for the cost-benefit model were calculated as the incremental cost of the new antiemetic regimen compared to the standard regimen. Costs from a payer perspective will include the acquisition cost of prophylactic antiemetic regimens. The net benefit of the intervention is calculated as the difference of incremental costs and benefits of the new antiemetic regimen compared to the standard regimen.

Net Benefit = Incremental benefits (valued as WTP) – Incremental costs

Sensitivity Analysis

One-way sensitivity analyses were conducted to test the robustness of the study results. The average WTP amounts were varied between the ±95% confidence limits of the WTP estimates. The impact of changes in the incremental costs of the antiemetic regimens on the net benefit was also studied.

CHAPTER FOUR

RESULTS

4.1: Results for Phase I

Phase I of the study involved constructing decision models to outline the costs and benefits associated with prophylactic antiemetic regimens for prevention of chemotherapy-induced nausea and vomiting (CINV) following highly emetogenic (HE) and moderately emetogenic (ME) chemotherapy. This section presents the results on total costs, total effectiveness and incremental cost-effectiveness ratios (ICER) of the different antiemetic regimens incorporated in the decision model.

For Highly Emetogenic Chemotherapy Decision Model – Base Case Analysis

Base Case Analysis Results – Without Side Effects of Regimens

A decision model was constructed to evaluate the total costs and benefits of four prophylactic antiemetic regimens for prevention of CINV due to HE chemotherapy (Refer Table 3-1). A hypothetical cohort of 10,000 cancer patients receiving HE chemotherapy was evaluated using first-order Monte Carlo simulation. The base case analysis was conducted based on the assumption that the probability of side effects due to regimen C is zero. The analysis was also performed for the decision model where the probability of side effects for regimen C was modeled and the results are reported later in the chapter. The costs from the payer's perspective include only the direct costs whereas both direct and indirect costs are included in the societal perspective.

The base case results for the costs, effectiveness, direct cost of achieving one patient with complete protection from emesis and the ICER for each of the four antiemetic regimens from the payer perspective are reported in Table 4-1.

Table 4-1: Base Case Results from Payer Perspective using Monte Carlo Simulation of 10,000 Patients with Cancer Receiving Highly Emetogenic Chemotherapy – Side Effects Not Modeled

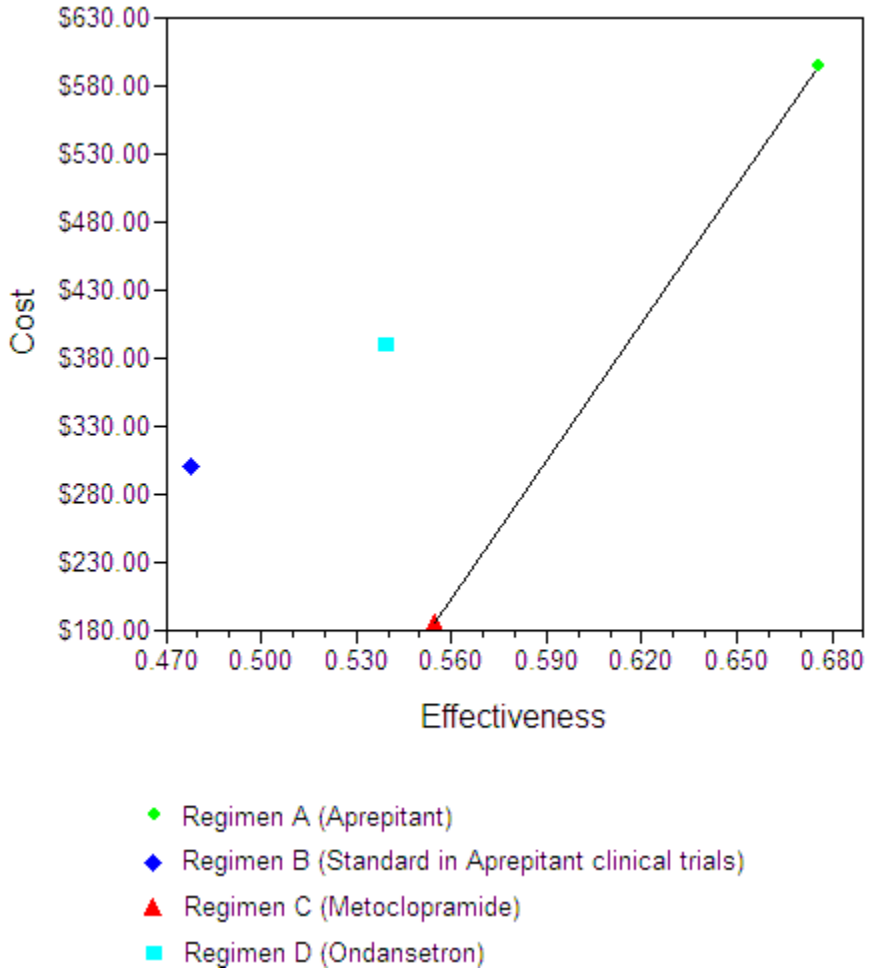
Treatment Strategy	**Side Effects Not Modeled**			
Payer Perspective	**Direct Costs Mean (SD)**	**Effectiveness Mean (SD)**	**Cost of achieving one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen C (Metoclopramide)	$187.18 ($33.37)	0.555 (0.497)	$337.26	-
Regimen B (Standard)	$300.53 ($36.69)	0.478 (0.499)	$628.72	Dominated[a]
Regimen D (Ondansetron)	$389.97 ($32.29)	0.539 (0.498)	$723.51	Dominated[a]
Regimen A (Aprepitant)	$593.45 ($27.02)	0.676 (0.468)	$877.88	$3,363.181/patient with complete control of emesis

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

[a]Dominated by regimen C

Regimen C, which includes metoclopramide as one of the antiemetic agents in the delayed phase, was the least expensive ($187.18 per patient for a period of 5 days) and regimen A (regimen with aprepitant) was the most expensive antiemetic treatment ($593.45) from the payer perspective. The direct costs of achieving one patient with complete protection from emesis with regimen A was found to be $877.88 which was approximately 1.2 times the direct cost of regimen D ($723.51) and approximately 2.6 times the total cost of regimen C ($337.26). The ICER for each treatment strategy was calculated to determine the additional cost per patient with complete control of emesis relative to the next costly option. Under the base-case assumptions using the direct costs, regimen A provided more health benefits and was more costly than regimen C, with a resulting ICER of $3,363.181 per patient with complete control of emesis. Regimens B and D were less effective and more costly than the base comparator, regimen C, i.e. regimens B and D are dominated by regimen C. The direct costs and effectiveness for the antiemetic regimens are represented graphically in figure 4-1 where the X-axis represents the effectiveness with respect to the probability of achieving patients with complete control of emesis, and the Y-axis represents costs in dollars.

Figure 4-1: Direct Costs and Effectiveness of Different Antiemetic Regimens for Patients Receiving Highly Emetogenic Chemotherapy from Payer Pespective – No Side Effects Modeled



The base case results for the total costs, effectiveness, total cost for achieving one patient with complete control of emesis and the ICER for each of the four antiemetic regimens from the societal perspective are also reported in Table 4-2. These results are represented graphically in figure 4-2. Similar to the results of the analysis from the payer perspective, regimen A was the most expensive treatment regimen ($658.97) followed by regimen D ($494.84), regimen B ($431.56) and regimen C ($295.89). The total costs of achieving a patient with complete protection from emesis with regimen A was found to be $963.41, which was approximately 1.8 times the total cost of the regimen C ($530.27). The ICER results show that the dominance status of the antiemetic regimens remained the same as in the analysis from the payer's perspective. The ICER of regimen A (regimen with aprepitant) compared with regimen C was $2,881 per patient with complete control of emesis. Regimens B and D had higher costs and lower effectiveness compared to regimen C and were thus said to be dominated by regimen C.

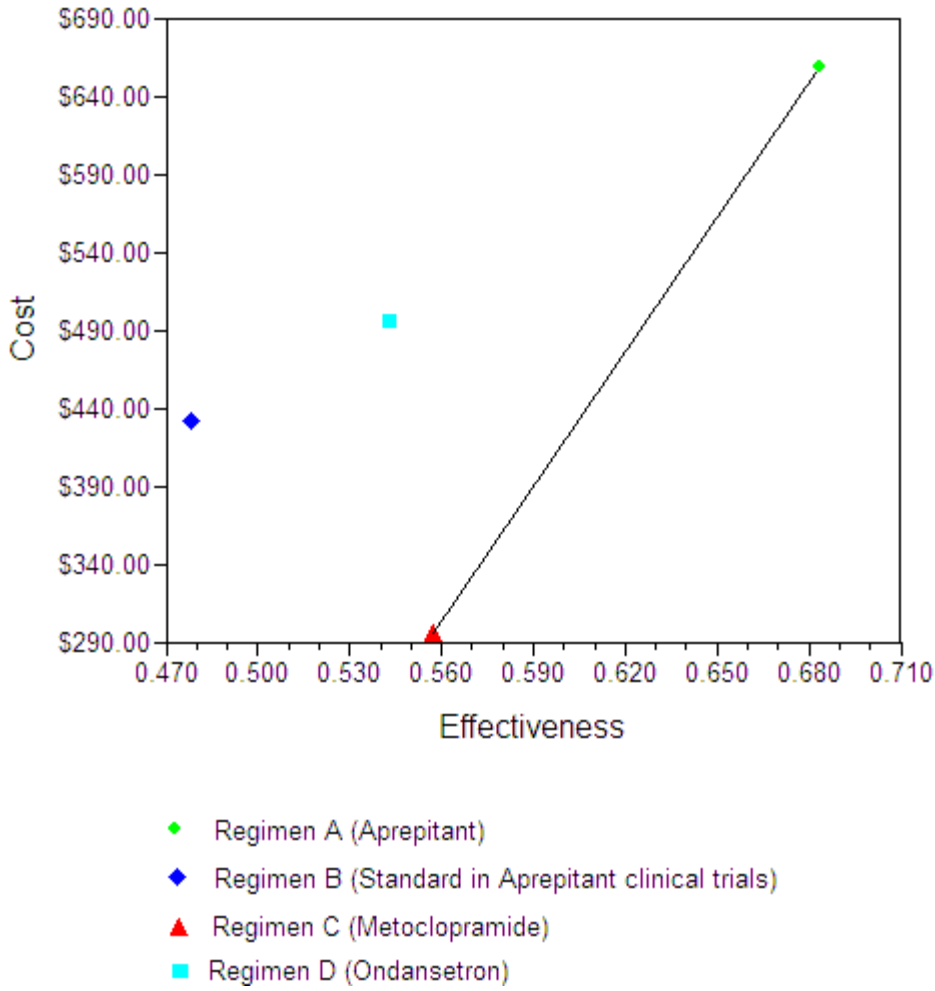
Table 4-2: Base Case Results from Societal Perspective using Monte Carlo Simulation of 10,000 Patients with Cancer Receiving Highly Emetogenic Chemotherapy – Side Effects Not Modeled

Treatment Strategy	**Side Effects Not Modeled**			
Societal Perspective	**Total Costs Mean (SD)**	**Effectiveness Mean (SD)**	**Cost of achieving one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen C (Metoclopramide)	$295.89 ($149.29)	0.558 (0.497)	$530.27	-
Regimen B (Standard)	$431.56 ($153.69)	0.478 (0.499)	$902.85	Dominated[a]
Regimen D (Ondansetron)	$494.84 ($148.27)	0.543 (0.498)	$911.31	Dominated[a]
Regimen A (Aprepitant)	$658.97 ($129.75)	0.684 (0.465)	$963.41	$2,881.605/patient with complete control of emesis

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

[a]Dominated by regimen C

Figure 4-2: Total Costs and Effectiveness of Different Antiemetic Regimens for Patients Receiving Highly Emetogenic Chemotherapy from Societal Perspective – No Side Effects Modeled



For Highly Emetogenic Chemotherapy Decision Model – Scenario Analysis

Impact of Side-Effects of Metoclopramide

In order to examine whether side effects due to metoclopramide affected the results of the decision model, the probability of experiencing the side effects and the costs associated with it were modeled. The mean costs, effectiveness, direct cost of achieving one patient with complete control of emesis and the ICER for each of the four antiemetic regimens from the payer perspective are reported in Table 4-3.

The mean direct costs were the highest for regimen A followed by regimens D, B and C. The mean direct costs associated with regimen C were $187.65 and the effectiveness was 0.542. The ICER results for the antiemetic regimens were sensitive to the changes, i.e. the inclusion of probabilities and costs due to side effects associated with regimen C. Regimen B was more costly and less effective as compared to regimen C and thus is said to be dominated by regimen C. Regimen D had higher costs and higher effectiveness compared to regimen C. However, regimen D also had a higher ICER compared to regimen A, which is more costly and more effective strategy than regimen D. Based on this, regimen C can be ruled out from the ICER calculations through extended dominance by a blend of regimen C and regimen A with a coefficient of inequity between 0.5 and 0.962. The ICER of regimen A compared with regimen C was $2,857.20 per patient with complete control of emesis. The results of this analysis from the payer's perspective are also presented in figure 4-3.

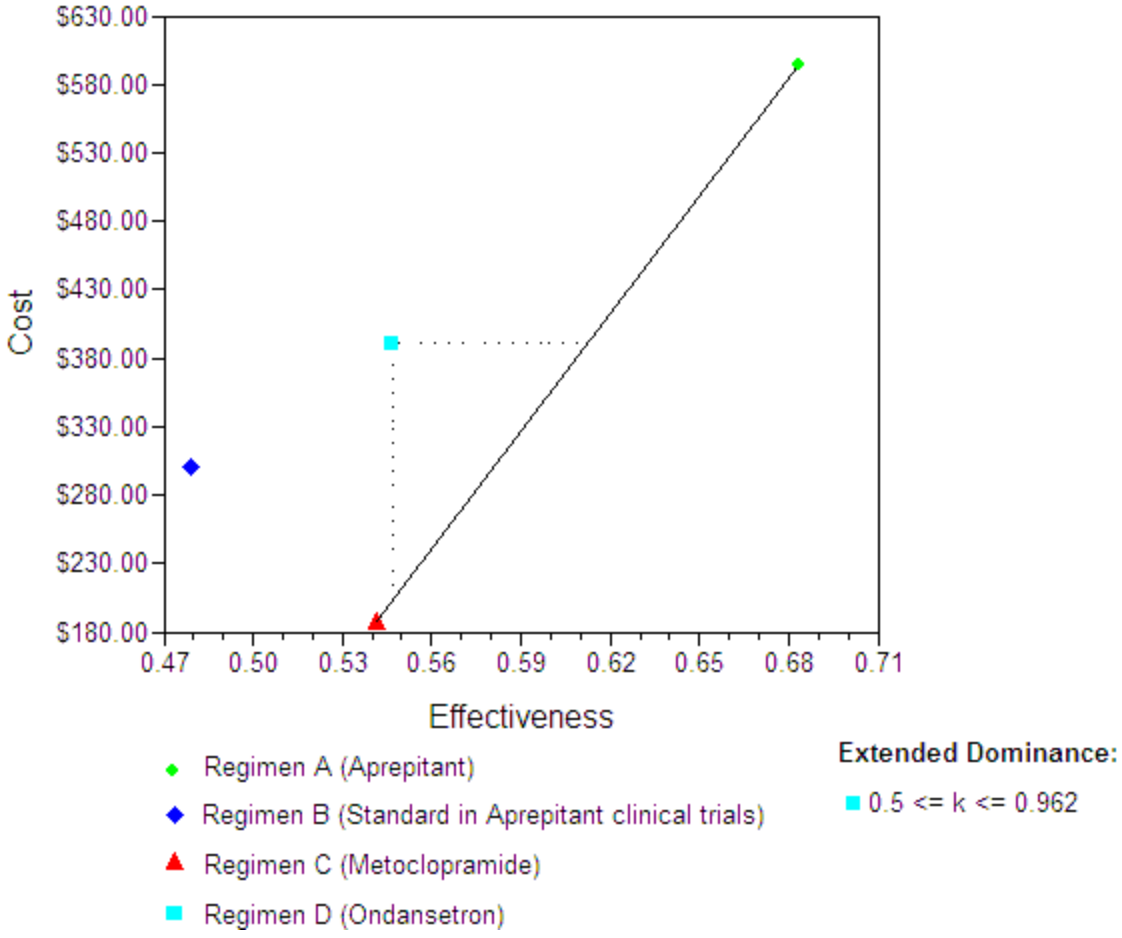
Table 4-3: Base Case Results from Payer Perspective using Monte Carlo Simulation of 10,000 Patients with Cancer Receiving Highly Emetogenic Chemotherapy – Side Effects Modeled

Treatment Strategy	**Side Effects Modeled**			
Payer Perspective	**Direct Costs Mean (SD)**	**Effectiveness Mean (SD)**	**Cost of achieving one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen C (Metoclopramide)	$187.65 ($34.90)	0.542 (0.498)	$346.22	-
Regimen B (Standard)	$300.68 ($37.12)	0.478 (0.499)	$629.04	Dominated*
Regimen D (Ondansetron)	$390.50 ($34.36)	0.547 (0.498)	$713.89	Extended Dominance**
Regimen A (Aprepitant)	$593.66 ($28.11)	0.684 (0.465)	$867.92	$2,857.20 per patient with complete control of emesis

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

* Regimen B dominated by regimen C
** Regimen D dominated by a blend of regimen C and regimen A with a coefficient of inequity between 0.50 and 0.962

Figure 4-3: Direct Costs, Effectiveness of Different Antiemetic Regimens for Patients Receiving Highly Emetogenic Chemotherapy from Payer Perspective – Side effects modeled



The mean costs, effectiveness, total cost of achieving one patient with complete control of emesis and the ICER for each of the four antiemetic regimens from the societal perspective are reported in Table 4-4. The mean total costs from the societal perspective were the highest for regimen A followed by regimens D, B and C. The mean total costs associated with regimen C were $659.30 and the effectiveness was 0.548. The ICER results for the antiemetic regimens were sensitive to the changes, i.e. the inclusion of probability and costs due to side effects associated with regimen C. Regimen B was more costly and less effective as compared to regimen C and thus is said to be dominated by regimen C. Regimen D had higher costs and higher effectiveness compared to regimen C but also had higher ICER compared to regimen A, which is more costly and more effective strategy than regimen D. Based on this, regimen C can be ruled out from the ICER calculations through extended dominance with a coefficient of inequity between 0.453 and 0.999. The ICER for regimen A compared to regimen C was found to be $2,731.09 per patient with complete control of emesis. The results of this analysis from the societal perspective are also presented in figure 4-4.

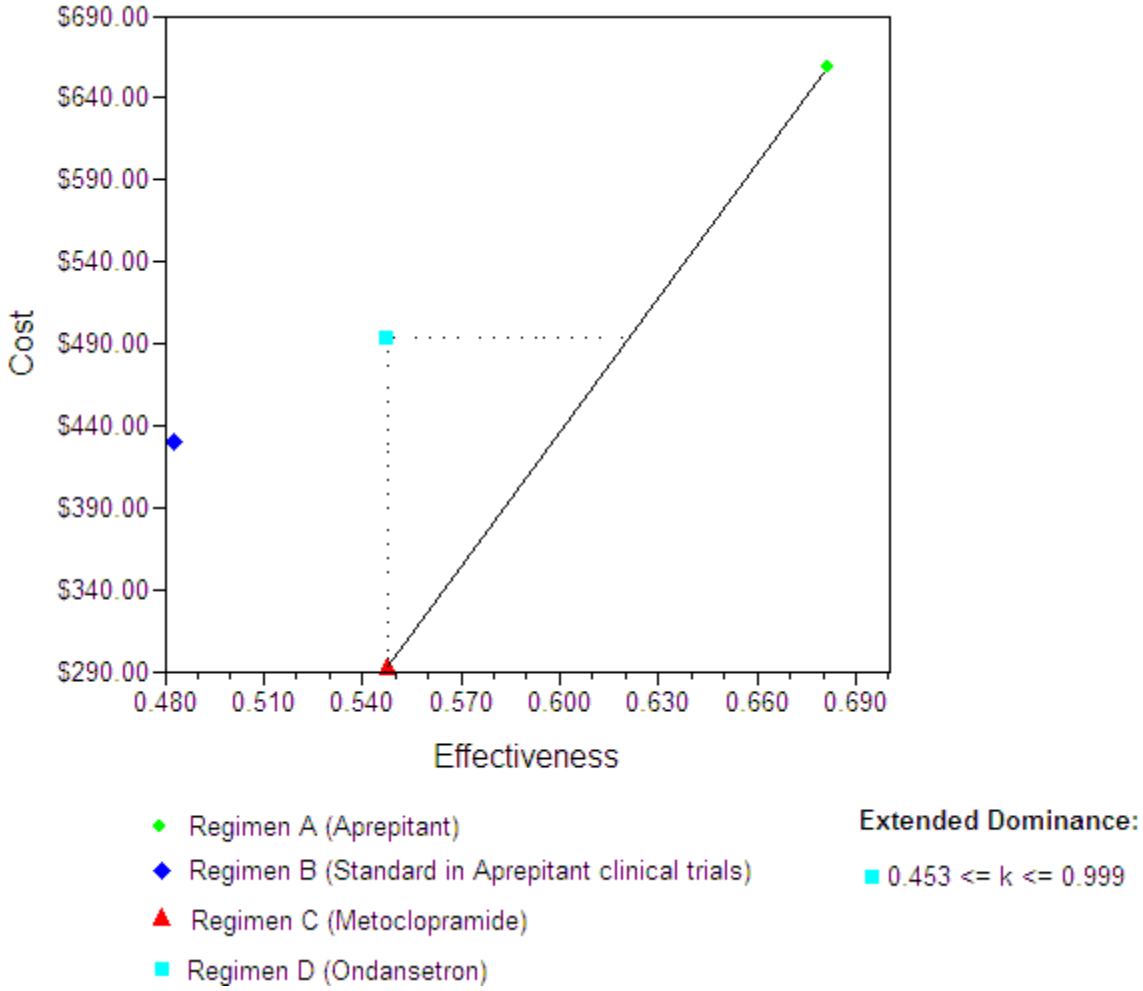
Table 4-4: Base Case Results from Societal Perspective using Monte Carlo Simulation of 10,000 Patients with Cancer Receiving Highly Emetogenic Chemotherapy – Side Effects Modeled

Treatment Strategy	**Side Effects Modeled**			
Societal Perspective	**Total Costs Mean (SD)**	**Effectiveness Mean (SD)**	**Cost of achieving one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen C (Metoclopramide)	$293.34 ($149.34)	0.548 (0.497)	$535.29	-
Regimen B (Standard)	$429.87 ($154.56)	0.482 (0.499)	$891.85	Dominated*
Regimen D (Ondansetron)	$493.43 ($148.25)	0.548 (0.498)	$900.42	Extended Dominance**
Regimen A (Aprepitant)	$659.30 ($129.91)	0.682 (0.465)	$966.72	$2,731.09 per patient with complete control of emesis

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

* Regimen B dominated by regimen C
** Regimen D dominated by a blend of regimen C and regimen A with a coefficient of inequity between 0.453 and 0.999

Figure 4-4: Total Costs, Effectiveness of Different Antiemetic Regimens for Patients Receiving Highly Emetogenic Chemotherapy from Societal Perspective – Side effects modeled



Sensitivity Analyses for Highly Emetogenic Chemotherapy Model

The estimates for the input parameters, both costs and effectiveness were derived and integrated from multiple sources. Thus, like any other economic model, the present model contains some degree of uncertainty. Sensitivity analysis is a commonly used tool to deal with uncertainty in the model input parameters. In one-way sensitivity analyses, one parameter at a time is varied over a certain range and the ICERs are recalculated. A comparison between the original ICER and those obtained from sensitivity analyses provide an indication of the stability of the model to changes in the values of the parameter.

Effect of Changes in Control of Acute and Delayed Emesis

The efficacy parameters, probability of no acute emesis, probability of no delayed emesis given no acute emesis and probability of no delayed emesis given acute emesis were varied over a plausible range obtained from published literature. Table 4-5 presents the range for sensitivity analysis and the direct costs and effectiveness from the payer's perspective. Table 4-6 presents the same results for the model from the societal perspective. The ICER for each regimen obtained from sensitivity analyses are reported in Table 4-7.

The change in the proportion of patients having no acute emesis has a significant impact on the effectiveness estimates for each regimen but a minor impact on the direct costs of each regimen. Although the dominance status of each regimen remained the same as in the base case analysis, the ICER of regimen A was extremely sensitive to the changes in the probability of no acute emesis for regimen A. For example, for the societal perspective, lowering the probability of no acute emesis of regimen A from 0.870 to 0.742 increased the ICER to $19,536.81 per patient with complete control of emesis and conversely, increasing the probability of no acute emesis of regimen A from 0.870 to 0.900 decreased the ICER to $2,521.81 per patient with complete control of emesis. Similar impact on ICER of regimen A was obtained for analysis conducted from payer perspective.

For the payer perspective, the changes in the probability of no delayed emesis given no acute emesis had a significant impact on the effectiveness of the considered treatment regimens but not on the costs. However, the same changes had a significant impact on both the effectiveness and cost estimates of each regimen for the analysis conducted from the societal

perspective. This is in part because in the societal perspective the indirect costs, which includes the work days lost due to uncontrolled delayed emesis, are taken into consideration. Thus, increasing the control of delayed emesis will result in lower work productivity losses and decreasing the control of delayed emesis will result in greater work productivity losses. The results in Table 4-7 show the ICER of each regimen for the higher and lower limits of the probability of no delayed emesis given no acute emesis. For changes in the ranges for regimens A, B and C, the dominance status of each regimen remains the same. However, the change in the parameter estimates of regimen D has an impact on the dominance status of the considered treatments. When the probability of no delayed emesis given no acute emesis for regimen D is increased from 0.715 to 0.858, regimen D has higher costs and higher effectiveness compared to regimen C, and thus is no longer dominated. Compared to regimen C, the ICER of regimen D is $2,173.07 per patient with complete control of emesis under the payer perspective and $1,787.86 per patient with complete control of emesis under the societal perspective. The ICER of regimen A compred to regimen D was $7.633.18 per patient with complete control of emesis from the payer perspective and $1,787.86 per patient with complete control of emesis from the societal perspective.

As indicated by the results, the effectiveness of each considered treatment was not sensitive to the changes in the probability of no delayed emesis given acute emesis. The robustness of the results is because effectiveness of each regimen is defined as no emesis in the acute and delayed phase and no rescue medications in the acute and delayed phases. Thus, any changes in the probability of no delayed emesis given acute emesis will not impact the effectiveness of each regimen. The changes in the base estimate of the parameter had a very slight impact on the costs of each regimen. The ICER results showed that the changes in the probability neither had a significant impact on the dominance status of the regimens nor on the ICER of regimen A.

Table 4-5: One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Payer Perspective – Efficacy Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of No Acute Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimens	**Range**								
Regimen A	0.742	$594.94	$300.71	$187.29	$390.26	0.578	0.477	0.558	0.542
	0.900	$593.11	$300.71	$187.29	$390.26	0.701	0.477	0.558	0.542
Regimen B	0.690	$593.46	$301.31	$187.29	$390.26	0.678	0.444	0.558	0.542
	0.793	$593.46	$300.12	$187.29	$390.26	0.678	0.510	0.558	0.542
Regimen C	0.742	$593.46	$300.71	$188.02	$390.84	0.678	0.477	0.518	0.504
	0.832	$593.46	$300.71	$186.86	$390.84	0.678	0.477	0.581	0.565
Regimen D	0.742	$593.46	$300.71	$188.02	$390.84	0.678	0.477	0.518	0.504
	0.832	$593.46	$300.71	$186.86	$390.84	0.678	0.477	0.581	0.565

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-5 (Continued): One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Payer Perspective– Efficacy Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of No Delayed Emesis Given No Acute Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimens	**Range**								
Regimen A	0.793	$593.99	$300.71	$187.29	$390.26	0.647	0.477	0.558	0.542
	0.866	$592.95	$300.71	$187.29	$390.26	0.707	0.477	0.558	0.542
Regimen B	0.646	$593.46	$300.99	$187.29	$390.26	0.678	0.460	0.558	0.542
	0.694	$593.46	$300.42	$187.29	$390.26	0.678	0.484	0.558	0.542
Regimen C	0.733	$593.46	$300.71	$187.33	$390.26	0.678	0.478	0.556	0.542
	0.738	$593.46	$300.71	$187.26	$390.26	0.678	0.478	0.560	0.542
Regimen D	0.572	$593.46	$300.71	$187.29	$392.10	0.678	0.477	0.558	0.434
	0.858	$593.46	$300.71	$187.29	$388.41	0.678	0.477	0.558	0.651

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-5 (Continued): One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Payer Perspective – Efficacy Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of No Delayed Emesis Given Acute Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimen	**Range**								
Regimen A	0.308	$593.48	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
	0.326	$593.44	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen B	0.122	$593.46	$300.84	$187.29	$390.26	0.678	0.477	0.558	0.542
	0.185	$593.46	$300.58	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen C	0.088	$593.46	$300.71	$187.47	$390.26	0.678	0.477	0.558	0.542
	0.200	$593.46	$300.71	$187.12	$390.26	0.678	0.477	0.558	0.542
Regimen D	0.228	$593.46	$300.71	$187.29	$390.45	0.678	0.477	0.558	0.542
	0.343	$593.46	$300.71	$187.29	$390.07	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-6: One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Societal Perspective – Efficacy Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of No Acute Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.742	$680.49	$431.74	$295.64	$495.29	0.578	0.478	0.558	0.542
	0.900	$655.72	$431.74	$295.64	$495.29	0.701	0.478	0.558	0.542
Regimen B	0.690	$660.43	$439.93	$295.64	$495.29	0.678	0.444	0.558	0.542
	0.793	$660.43	$423.71	$295.64	$495.29	0.678	0.510	0.558	0.542
Regimen C	0.742	$660.43	$431.74	$305.92	$502.79	0.678	0.478	0.519	0.504
	0.832	$660.43	$431.74	$289.69	$490.94	0.678	0.478	0.581	0.565
Regimen D	0.742	$660.43	$431.74	$305.92	$502.79	0.678	0.478	0.519	0.504
	0.832	$660.43	$431.74	$289.69	$490.94	0.678	0.478	0.581	0.565

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-6 (Continued): One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Societal Perspective – Efficacy Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Probability of No Delayed Emesis Given No Acute Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.793	$670.06	$431.74	$295.64	$495.29	0.648	0.478	0.558	0.542
	0.866	$651.05	$431.74	$295.64	$495.29	0.707	0.478	0.558	0.542
Regimen B	0.646	$660.43	$437.06	$295.64	$495.27	0.678	0.460	0.558	0.542
	0.694	$660.43	$426.41	$295.64	$495.27	0.678	0.494	0.558	0.542
Regimen C	0.733	$660.43	$431.74	$296.36	$495.29	0.678	0.478	0.556	0.542
	0.738	$660.43	$431.74	$295.17	$495.29	0.678	0.478	0.560	0.542
Regimen D	0.572	$660.43	$431.74	$295.64	$529.46	0.678	0.478	0.558	0.434
	0.858	$660.43	$431.74	$295.64	$461.11	0.678	0.478	0.558	0.651

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-6 (Continued): One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Societal Perspective – Efficacy Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Probability of No Delayed Emesis Given Acute Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.308	$660.78	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
	0.326	$660.08	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen B	0.122	$660.43	$434.20	$295.64	$495.29	0.678	0.477	0.558	0.542
	0.185	$660.43	$429.35	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen C	0.088	$660.43	$431.74	$299.01	$495.29	0.678	0.477	0.558	0.542
	0.200	$660.43	$431.74	$292.28	$495.29	0.678	0.477	0.558	0.542
Regimen D	0.228	$660.43	$431.74	$295.64	$498.77	0.678	0.477	0.558	0.542
	0.343	$660.43	$431.74	$295.64	$491.86	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-7: One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Payer and Societal Perspective – ICERs for Efficacy Parameters

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Probability of No Acute Emesis							
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Regimens	**Range**						
Regimen A	0.742	$20,694.99	Dominated[a]	Dominated[a]	$19,536.81	Dominated[a]	Dominated[a]
	0.900	$2,842.19	Dominated[a]	Dominated[a]	$2,521.81	Dominated[a]	Dominated[a]
Regimen B	0.690	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.793	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.742	$2,545.98	Dominated[a]	Dominated[a]	$2,226.10	Dominated[a]	Dominated[a]
	0.832	$4,219.81	Dominated[a]	Dominated[a]	$3,847.59	Dominated[a]	Dominated[a]
Regimen D	0.742	$2,545.98	Dominated[a]	Dominated[a]	$2,226.10	Dominated[a]	Dominated[a]
	0.832	$4,219.81	Dominated[a]	Dominated[a]	$3,847.59	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4);
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatments are compared to Regimen C
[a] Dominated by regimen C

Table 4-7 (Continued): One Way Sensitivity Analyses Results For Highly Emetogenic Chemotherapy Model with No Side Effects from Payer and Societal Perspective – ICERs for Efficacy Parameters

Parameters/Range		**ICER per patient with complete control of emesis – Payer Perspective**			**ICER per patient with complete control of emesis – Societal Perspective**		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Probability of No Delayed Emesis Given No Acute Emesis							
Regimen A	0.793	$4,559.31	Dominated[a]	Dominated[a]	$4,197.39	Dominated[a]	Dominated[a]
	0.866	$2,726.00	Dominated[a]	Dominated[a]	$2,388.31	Dominated[a]	Dominated[a]
Regimen B	0.646	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.694	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.733	$3,337.42	Dominated[a]	Dominated[a]	$2,991.71	Dominated[a]	Dominated[a]
	0.738	$3,445.34	Dominated[a]	Dominated[a]	$3,098.10	Dominated[a]	Dominated[a]
Regimen D	0.572	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.858	$7,633.18	Dominated[a]	$2,173.08	$7,419.57	Dominated[a]	$1,787.86

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatments are compared to Regimen C
[a] Dominated by regimen C

Table 4-7 (Continued): One Way Sensitivity Analyses Results for Highly Emetogenic Chemotherapy Model with No Side Effects from Payer and Societal Perspective – ICERs for Efficacy Parameters

Parameters/Range		**ICER per patient with complete control of emesis – Payer Perspective**			**ICER per patient with complete control of emesis – Societal Perspective**		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Base Case		$3,363.181	Dominated[a]	Dominated	$2,881.605	Dominated[a]	Dominated[a]
Probability of No Delayed Emesis Given Acute Emesis							
Regimen A	0.308	$3,401.51	Dominated[a]	Dominated[a]	$3,057.66	Dominated[a]	Dominated[a]
	0.326	$3,401.19	Dominated[a]	Dominated[a]	$3,051.80	Dominated[a]	Dominated[a]
Regimen B	0.122	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.185	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.088	$3,399.83	Dominated[a]	Dominated[a]	$3,026.54	Dominated[a]	Dominated[a]
	0.200	$3,402.87	Dominated[a]	Dominated[a]	$3,082.92	Dominated[a]	Dominated[a]
Regimen D	0.228	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.343	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatments are compared to Regimen C
[a] Dominated by regimen C

Effect of Changes in the Receipt of Rescue Medications

The parameters, probability of receiving rescue medications in the acute phase given no acute emesis and given acute emesis and probability of receiving rescue medications in the delayed phase given no delayed emesis and given delayed emesis were varied over a plausible range shown in Chapter 3, Table 3-6. Table 4-8 presents the range for each parameter for each regimen and the direct costs and effectiveness estimates from the payer's perspective. Table 4-9 presents the results from the societal perspective. The ICER for each regimen obtained from sensitivity analyses are reported in Table 4-10.

As evident from Tables 4-8 and 4-9, the changes in the probability of receiving rescue medications in the acute phase given no acute emesis for each regimen had an impact on the effectiveness results for that regimen but no significant impact on the costs. The dominance status of each considered treatment remained the same as in base case but resulted in changes in the ICERs of regimen A. Decreasing the proportion of patients receiving rescue medications for no acute emesis for regimen A to zero resulted in an ICER of $3,181.86 per patient with complete control of emesis from payer's perspective and $2,857.60 from the societal perspective. Conversely, for other regimens, decreasing the proportion of patients receiving rescue medications for no acute emesis to zero resulted in an increased ICER for regimen A.

The costs, effectiveness and ICER results were not sensitive to changes in the probabilities of receipt of rescue medications in the acute phase given acute emesis and receipt of rescue medications in the delayed phase given delayed emesis. From the payer and societal perspectives, the costs, effectiveness and ICER results for the alternative regimens were sensitive to the changes in the probability of receipt of rescue medications in the delayed phase given no delayed emesis. Decreasing the probability of receipt of rescue medications in the delayed phase given no delayed emesis for regimen A resulted in decreasing the ICER to $2,615.75 and $2,348.85, for the payer and societal perspective respectively. Increasing the probability of receipt of rescue medications in the delayed phase given no delayed emesis for regimen A resulted in increasing the ICER to $3,506.52 and $3,149.23 for the payer and societal perspective, respectively. The changes in this probability for regimen D resulted in a change in the dominance status of the antiemetic regimens. When the probability of receiving rescue medications for regimen D was set at zero, the ICER from societal perspective for regimen A increased to $3,054.73 and regimen D was ruled out by extended dominance status (Table 4-10).

Effect of Changes in the Receipt of Outpatient Care

The impact of changes in the probability of receiving outpatient care during the acute phase and delayed phase, either with no rescue medications or with rescue medications, on direct costs, total costs, effectiveness and ICERs are presented in Tables 4-8, 4-9 and 4-10. The results show that the baseline estimates were not sensitive to the changes in the probability of receipt of outpatient care during either the acute or delayed phase. The dominance status of the antiemetic regimens remained the same, from the payer and societal perspectives, as in the base-case analysis.

Table 4-8: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given No Acute Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimens	**Range**								
Regimen A	0.000	$593.44	$300.71	$187.29	$390.26	0.686	0.477	0.558	0.542
	0.015	$593.47	$300.71	$187.29	$390.26	0.676	0.477	0.558	0.542
Regimen B	0.000	$593.46	$300.69	$187.29	$390.26	0.678	0.483	0.558	0.542
	0.015	$593.46	$300.71	$187.29	$390.26	0.678	0.476	0.558	0.542
Regimen C	0.000	$593.46	$300.71	$187.27	$390.24	0.678	0.477	0.565	0.549
	0.015	$593.46	$300.71	$187.29	$390.26	0.678	0.477	0.557	0.541
Regimen D	0.000	$593.46	$300.71	$187.27	$390.24	0.678	0.477	0.565	0.549
	0.015	$593.46	$300.71	$187.29	$390.26	0.678	0.477	0.557	0.541

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-8 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receipt of Rescue Medications in the Acute Phase Given Acute Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimens	**Range**								
Regimen A	0.175	$593.43	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
	1.000	$593.60	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen B	0.304	$593.46	$300.67	$187.29	$390.26	0.678	0.477	0.558	0.542
	1.000	$593.46	$300.96	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen C	0.304	$593.46	$300.71	$187.26	$390.23	0.678	0.477	0.558	0.542
	1.000	$593.46	$300.71	$187.49	$390.46	0.678	0.477	0.558	0.542
Regimen D	0.304	$593.46	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
	1.000	$593.46	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-8 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

Parameters/Range		**DIRECT COSTS**				**EFFECTIVENESS**			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receipt of Rescue Medications in the Delayed Phase Given No Delayed Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimens	**Range**								
Regimen A	0.000	$592.96	$300.71	$187.29	$390.26	0.713	0.477	0.558	0.542
	0.055	$593.51	$300.71	$187.29	$390.26	0.674	0.477	0.558	0.542
Regimen B	0.000	$594.46	$300.51	$187.29	$390.26	0.678	0.491	0.558	0.542
	0.035	$594.46	$300.76	$187.29	$390.26	0.678	0.474	0.558	0.542
Regimen C	0.000	$593.46	$300.71	$186.97	$390.26	0.678	0.477	0.581	0.542
	0.045	$593.46	$300.71	$187.34	$390.26	0.678	0.477	0.555	0.542
Regimen D	0.000	$593.46	$300.71	$187.29	$389.93	0.678	0.477	0.558	0.564
	0.045	$593.46	$300.71	$187.29	$390.31	0.678	0.477	0.558	0.539

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-8 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receipt of Rescue Medications in the Delayed Phase Given Delayed Emesis									
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Regimens	**Range**								
Regimen A	0.454	**$593.08**	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
	1.000	**$594.79**	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen B	0.477	$593.46	**$300.38**	$187.29	$390.26	0.678	0.477	0.558	0.542
	1.000	$593.46	**$303.58**	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen C	0.465	$593.46	$300.71	**$186.84**	$390.26	0.678	0.477	0.558	0.542
	1.000	$593.46	$300.71	**$189.55**	$390.26	0.678	0.477	0.558	0.542
Regimen D	0.465	$593.46	$300.71	$187.29	**$389.83**	0.678	0.477	0.558	0.542
	1.000	$593.46	$300.71	$187.29	**$392.45**	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-8 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Receipt of Outpatient Care

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Parameter: Probability of Receipt of Outpatient Care During Acute Phase Given:									
No Rescue Medications	0.000	$593.23	$300.29	$186.96	$389.93	0.678	0.477	0.558	0.542
	0.030	$593.92	$301.54	$187.94	$390.91	0.678	0.477	0.558	0.542
Rescue Medications	0.000	$593.34	$300.44	$187.08	$390.05	0.678	0.477	0.558	0.542
	0.030	$593.70	$301.25	$$187.71	$390.68	0.678	0.477	0.558	0.542
Parameter: Probability of Receipt of Outpatient Care During Delayed Phase Given:									
No Rescue Medications	0.02	$593.06	$299.84	$186.60	$389.59	0.678	0.477	0.558	0.542
	0.05	$593.86	$301.58	$187.97	$390.92	0.678	0.477	0.558	0.542
Rescue Medications	0.02	$592.91	$$299.72	$186.44	$389.43	0.678	0.477	0.558	0.542
	0.05	$594.00	$301.69	$188.14	$391.08	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4);
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-9: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given No Acute Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.000	$660.41	$431.74	$295.64	$495.29	0.686	0.477	0.558	0.542
	0.015	$660.41	$431.74	$295.64	$495.29	0.676	0.477	0.558	0.542
Regimen B	0.000	$660.43	$431.72	$295.64	$495.29	0.678	0.483	0.558	0.542
	0.015	$660.43	$431.74	$295.64	$495.29	0.678	0.476	0.558	0.542
Regimen C	0.000	$660.43	$431.74	$295.63	$495.27	0.678	0.477	0.565	0.549
	0.015	$660.43	$431.74	$295.65	$495.29	0.678	0.477	0.557	0.541
Regimen D	0.000	$660.43	$431.74	$295.63	$495.27	0.678	0.477	0.565	0.549
	0.015	$660.43	$431.74	$295.65	$495.29	0.678	0.477	0.557	0.541

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-9 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receipt of Rescue Medications in the Acute Phase Given Acute Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.175	$660.39	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
	1.000	$660.57	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen B	0.304	$660.43	$431.70	$295.64	$495.29	0.678	0.477	0.558	0.542
	1.000	$660.43	$431.99	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen C	0.304	$660.43	$431.74	$295.61	$495.26	0.678	0.477	0.558	0.542
	1.000	$660.43	$431.74	$295.84	$495.49	0.678	0.477	0.558	0.542
Regimen D	0.304	$660.43	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
	1.000	$660.43	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-9 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receipt of Rescue Medications in the Delayed Phase Given No Delayed Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.000	$659.92	$431.74	$295.64	$495.29	0.713	0.477	0.558	0.542
	0.055	$660.48	$431.74	$295.64	$495.29	0.674	0.477	0.558	0.542
Regimen B	0.000	$660.43	$431.54	$295.64	$495.29	0.678	0.491	0.558	0.542
	0.035	$660.43	$431.79	$295.64	$495.29	0.678	0.474	0.558	0.542
Regimen C	0.000	$660.43	$431.74	$295.33	$495.29	0.678	0.477	0.581	0.542
	0.045	$660.43	$431.74	$295.69	$495.29	0.678	0.477	0.555	0.542
Regimen D	0.000	$660.43	$431.74	$295.64	$494.96	0.678	0.477	0.558	0.564
	0.045	$660.43	$431.74	$295.64	$495.34	0.678	0.477	0.558	0.539

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-9 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Parameter: Probability of Receipt of Rescue Medications in the Delayed Phase Given Delayed Emesis									
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Regimens	**Range**								
Regimen A	0.454	$660.04	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
	1.000	$661.75	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen B	0.477	$660.43	$431.41	$295.64	$495.29	0.678	0.477	0.558	0.542
	1.000	$660.43	$434.61	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen C	0.465	$660.43	$431.74	$295.20	$495.29	0.678	0.477	0.558	0.542
	1.000	$660.43	$431.74	$297.91	$495.29	0.678	0.477	0.558	0.542
Regimen D	0.465	$660.43	$431.74	$295.64	$494.85	0.678	0.477	0.558	0.542
	1.000	$660.43	$431.74	$295.64	$497.48	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-9 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Receipt of Outpatient Care

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Parameter: Probability of Receipt of Outpatient Care During Acute Phase Given:									
No Rescue Medications	0.000	$660.20	$431.32	$295.32	$494.96	0.678	0.477	0.558	0.542
	0.030	$660.89	$432.57	$296.30	$495.94	0.678	0.477	0.558	0.542
Rescue Medications	0.000	$660.31	$431.46	$295.43	$495.06	0.678	0.477	0.558	0.542
	0.030	$660.66	$432.28	$296.07	$495.71	0.678	0.477	0.558	0.542
Probability of Receipt of Outpatient Care During Delayed Phase Given:									
No Rescue Medications	0.02	$660.02	$430.87	$294.96	$494.62	0.678	0.477	0.558	0.542
	0.05	$660.83	$432.61	$296.33	$495.95	0.678	0.477	0.558	0.542
Rescue Medications	0.02	$659.88	$430.75	$294.79	$494.46	0.678	0.477	0.558	0.542
	0.05	$660.97	$432.72	$296.49	$496.11	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4);
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-10: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given No Acute Emesis							
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Regimens	**Range**						
Regimen A	0.000	$3,181.86	Dominated[a]	Dominated[a]	$2,857.60	Dominated[a]	Dominated[a]
	0.015	$3,461.03	Dominated[a]	Dominated[a]	$3,108.34	Dominated[a]	Dominated[a]
Regimen B	0.000	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.015	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.000	$3,606.28	Dominated[a]	Dominated[a]	$3,238.79	Dominated[a]	Dominated[a]
	0.015	$3,353.70	Dominated[a]	Dominated[a]	$3,011.94	Dominated[a]	Dominated[a]
Regimen D	0.000	$3,606.28	Dominated[a]	Dominated[a]	$3,238.79	Dominated[a]	Dominated[a]
	0.015	$3,353.70	Dominated[a]	Dominated[a]	$3,011.94	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
[a] Dominated by regimen C
All treatments are compared to Regimen C

Table 4-10 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given Acute Emesis							
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Regimens	**Range**						
Regimen A	0.175	$3,401.06	Dominated[a]	Dominated[a]	$3,054.44	Dominated[a]	Dominated[a]
	1.000	$3,402.54	Dominated[a]	Dominated[a]	$3,055.92	Dominated[a]	Dominated[a]
Regimen B	0.304	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	1.000	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.304	$3,401.60	Dominated[a]	Dominated[a]	$3,054.98	Dominated[a]	Dominated[a]
	1.000	$3,399.68	Dominated[a]	Dominated[a]	$3,053.05	Dominated[a]	Dominated[a]
Regimen D	0.304	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	1.000	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1) , Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
[a] Dominated by regimen C
All treatments are compared to Regimen C

Table 4-10 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Parameter: Probability of Receiving Rescue Medications In the Delayed Phase Given No Delayed Emesis							
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Regimens	**Range**						
Regimen A	0.000	$2,615.75	Dominated[a]	Dominated[a]	$2,348.85	Dominated[a]	Dominated[a]
	0.055	$3,506.52	Dominated[a]	Dominated[a]	$3,149.23	Dominated[a]	Dominated[a]
Regimen B	0.000	$3.401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	0.035	$3.401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.000	$4,201.21	Dominated[a]	Dominated[a]	$3,733.41	Dominated[a]	Dominated[a]
	0.045	$3,304.48	Dominated[a]	Dominated[a]	$2,967.69	Dominated[a]	Dominated[a]
Regimen D	0.000	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Extended Dominance[b]
	0.045	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4);
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatments are compared to Regimen C
[a] Dominated by regimen C
[b] Regimen D is dominated by a blend of regimens C and A

Table 4-10 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Parameter: Probability of Receiving Rescue Medications In the Delayed Phase Given Delayed Emesis							
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Regimens	**Range**						Dominated[a]
Regimen A	0.454	$3,398.15	Dominated[a]	Dominated[a]	$3,051.53	Dominated[a]	Dominated[a]
	1.000	$3,412.47	Dominated[a]	Dominated[a]	$3,065.85	Dominated[a]	Dominated[a]
Regimen B	0.477	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	1.000	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
Regimen C	0.465	$3,405.09	Dominated[a]	Dominated[a]	$3,058.46	Dominated[a]	Dominated[a]
	1.000	$3,382.39	Dominated[a]	Dominated[a]	$3,035.77	Dominated[a]	Dominated[a]
Regimen D	0.465	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]
	1.000	$3,401.35	Dominated[a]	Dominated[a]	$3,054.73	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4)
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4)
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatments are compared to Regimen C
[a] Dominated by regimen C

Table 4-10 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Outpatient Care

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated[a]
Parameter: Probability of Receipt of Outpatient Care During Acute Phase Given:							
No Rescue Medications	0.000	$3,402.15	Dominated[a]	Dominated[a]	$3,055.53	Dominated[a]	Dominated[a]
	0.030	$3,399.75	Dominated[a]	Dominated[a]	$3,053.13	Dominated[a]	Dominated[a]
Rescue Medications	0.000	$3,402.14	Dominated[a]	Dominated[a]	$3,055.52	Dominated[a]	Dominated[a]
	0.030	$3,399.77	Dominated[a]	Dominated[a]	$3,053.15	Dominated[a]	Dominated[a]
Parameter: Probability of Receipt of Outpatient Care During Delayed Phase Given:							
No Rescue Medications	0.02	$3,403.73	Dominated[a]	Dominated[a]	$3,057.11	Dominated[a]	Dominated[a]
	0.05	$3,398.97	Dominated[a]	Dominated[a]	$3,052.35	Dominated[a]	Dominated[a]
Rescue Medications	0.02	$3,403.89	Dominated[a]	Dominated[a]	$3,057.27	Dominated[a]	Dominated[a]
	0.05	$3,398.82	Dominated[a]	Dominated[a]	$3,052.20	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4);
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4).
All treatments are compared to Regimen C

Effect of Changes in Cost and Utilization Parameters

The impact of changes in the cost of antiemetic drugs and antiemetic regimens, infusion costs, and number of days for which rescue medications were received, on costs and effectiveness are reported in Tables 4-11 and 4-12. The impacts of changes in the parameters on the ICER of each treatment regimen are presented in Table 4-13. The total costs of the prophylactic antiemetic regimens were varied between plus 20% and minus 20% of the base-case estimates.

The variations in the costs did not change the dominance status of the individual antiemetic regimens. Increasing the total cost of regimen A by 20% increases the ICER for regimen A to $4,386.99 per patient with complete control of emesis from a payer perspective, and to $2,415.71 per patient with complete control of emesis from a societal perspective. For analysis conducted from payer perspective, a 20% increase in the cost of aprepitant increased the ICER of regimen A by approximately $555 per patient with complete control of emesis, while a 20% decrease in the cost of aprepitant decreased the ICER of the regimen by approximately by $480 per patient with complete control of emesis. The dominance status of each considered regimen remained the same as in the base-case analysis. The results were not sensitive to the changes in the cost of intravenous ondansetron, infusion costs and the number of days for which rescue medications given during the delayed phase.

Table 4-11: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Cost Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Parameter: Total Prophylactic Antiemetic Regimen Costs									
Regimen	**Range**								
Regimen A	$470.80	$475.76	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
	$760.20	$652.31	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen B	$233.64	$593.46	$242.30	$187.29	$390.26	0.678	0.477	0.558	0.542
	$350.46	$593.46	$359.12	$187.29	$390.26	0.678	0.477	0.558	0.542
Regimen C	$143.92	$593.46	$300.71	$151.31	$390.26	0.678	0.477	0.558	0.542
	$215.88	$593.46	$300.71	$223.27	$390.26	0.678	0.477	0.558	0.542
Regimen D	$306.45	$593.46	$300.71	$187.29	$313.65	0.678	0.477	0.558	0.542
	$459.67	$593.46	$300.71	$187.29	$466.87	0.678	0.477	0.558	0.542
Parameter: Cost of Aprepitant									
Aprepitant	$247.22	$531.70	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542
	$370.80	$655.30	$300.71	$187.29	$390.26	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-11 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Cost Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		$593.45	$300.53	$187.18	$389.97	0.676	0.478	0.555	0.539
Parameter: Cost of IV Ondansetron									
Ondansetron	$165.13	$552.08	$259.23	$176.87	$379.84	0.678	0.477	0.558	0.542
	$247.69	$634.84	$342.18	$197.71	$400.67	0.678	0.477	0.558	0.542
Parameter: Infusion Costs									
First Drug	$47.16	$581.56	$288.70	$175.32	$378.29	0.678	0.477	0.558	0.542
	$70.74	$605.36	$312.72	$199.26	$402.22	0.678	0.477	0.558	0.542
Second Drug	$22.18	$593.46	$300.71	$181.75	$384.72	0.678	0.477	0.558	0.542
	$33.26	$593.46	$300.71	$192.83	$395.80	0.678	0.477	0.558	0.542
Parameter: Number of Days of Receiving Rescue Medications During Delayed Phase									
No. of Days	1 day	$592.89	$299.85	$186.51	$389.50	0.678	0.477	0.558	0.542
	3 days	$594.03	$301.57	$188.06	$391.01	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-12: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Cost Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		$658.97	$431.56	$295.89	$494.84	0.684	0.478	0.558	0.543
Parameter: Total Prophylactic Antiemetic Regimen Costs									
Regimen	**Range**								
Regimen A	$470.80	$542.73	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
	$760.20	$778.13	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen B	$233.64	$660.43	$373.33	$295.64	$495.29	0.678	0.477	0.558	0.542
	$350.46	$660.43	$490.15	$295.64	$495.29	0.678	0.477	0.558	0.542
Regimen C	$143.92	$660.43	$431.74	$259.66	$495.29	0.678	0.477	0.558	0.542
	$215.88	$660.43	$431.74	$331.62	$495.29	0.678	0.477	0.558	0.542
Regimen D	$306.45	$660.43	$431.74	$295.64	$418.68	0.678	0.477	0.558	0.542
	$459.67	$660.43	$431.74	$295.64	$571.90	0.678	0.477	0.558	0.542
Parameter: Cost of Aprepitant									
Aprepitant	$247.22	$598.60	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542
	$370.80	$722.20	$431.74	$295.64	$495.29	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-12 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Cost Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		**$658.97**	**$431.56**	**$295.89**	**$494.84**	**0.684**	**0.478**	**0.558**	**0.543**
Parameter: Cost of IV Ondansetron									
Ondansetron	$165.13	**$619.05**	$390.26	$285.23	$484.87	0.678	0.477	0.558	0.542
	$247.69	**$701.80**	$473.21	$306.06	$505.70	0.678	0.477	0.558	0.542
Parameter: Infusion Costs									
First Drug	$47.16	$648.52	**$419.72**	$283.67	$483.32	0.678	0.477	0.558	0.542
	$70.74	$672.33	$443.75	**$307.62**	$507.25	0.678	0.477	0.558	0.542
Second Drug	$22.18	$660.43	$431.74	**$290.10**	$489.75	0.678	0.477	0.558	0.542
	$33.26	$660.43	$431.74	$301.18	**$500.83**	0.678	0.477	0.558	0.542
Parameter: Number of Days of Receiving Rescue Medications During Delayed Phase									
No. of Days	1 day	**$659.85**	$430.88	$294.87	$494.53	0.678	0.477	0.558	0.542
	3 days	**$661.00**	$432.59	$296.42	$496.04	0.678	0.477	0.558	0.542

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-13: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Cost Parameters

		ICER per patient with complete control of emesis – Payer Perspective			ICER per patient with complete control of emesis – Societal Perspective		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Base Case		$3,363.181	Dominated[a]	Dominated[a]	$2,881.605	Dominated[a]	Dominated
Parameter: Total Prophylactic Antiemetic Regimen Costs							
Regimen	**Range**						
Regimen A	$470.80	$2,415.71	Dominated[a]	Dominated[a]	$2,069.09	Dominated[a]	Dominated[a]
	$760.20	$4,386.99	Dominated[a]	Dominated[a]	$4,040.37	Dominated[a]	Dominated[a]
Regimen B	$233.64	$3,401.35	Dominated[a]	Dominated[a]	$3,054,73	Dominated[a]	Dominated[a]
	$350.46	$3,401.35	Dominated[a]	Dominated[a]	$3,054,73	Dominated[a]	Dominated[a]
Regimen C	$143.92	$,3702.65	Dominated[a]	Dominated[a]	$3,356.03	Dominated[a]	Dominated[a]
	$215.88	$3,100.05	Dominated[a]	Dominated[a]	$2,753.43	Dominated[a]	Dominated[a]
Regimen D	$306.45	$3,401.35	Dominated[a]	Dominated[a]	$3,054,73	Dominated[a]	Dominated[a]
	$459.67	$3,401.35	Dominated[a]	Dominated[a]	$3,054,73	Dominated[a]	Dominated[a]
Parameter: Cost of Aprepitant							
Aprepitant	$247.22	$2,883.91	Dominated[a]	Dominated[a]	$2,537.29	Dominated[a]	Dominated[a]
	$370.80	$3,918.79	Dominated[a]	Dominated[a]	$3,572.17	Dominated[a]	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4);
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Table 4-13 (Continued): One Way Sensitivity Analyses Results For HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Cost Parameters

Parameters/Range		**ICER – Payer Perspective**			**ICER – Societal Perspective**		
		Regimen A	**Regimen B**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen D**
Base Case		$3,363.181	Dominated	Dominated	$2,881.605	Dominated	Dominated
Parameter: Cost of IV Ondansetron							
Ondansetron	$165.13	$3,142.09	Dominated	Dominated	$2,795.47	Dominated	Dominated
	$247.69	$3,660.62	Dominated	Dominated	$3,314.00	Dominated	Dominated
Parameter: Infusion Costs							
First Drug	$47.16	$3,401.93	Dominated	Dominated	$3,055.31	Dominated	Dominated
	$70.74	$3,400.78	Dominated	Dominated	$3,054.16	Dominated	Dominated
Second Drug	$22.18	$3,447.74	Dominated	Dominated	$3,101.12	Dominated	Dominated
	$33.26	$3,354.96	Dominated	Dominated	$3,008.34	Dominated	Dominated
Parameter: Number of Days of Receiving Rescue Medications During Delayed Phase							
No. of Days	1 day	$3,403.04	Dominated	Dominated	$3,056.42	Dominated	Dominated
	3 days	$3,399.66	Dominated	Dominated	$3,053.04	Dominated	Dominated

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4); **Regimen B**: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4); **Regimen D**: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)

Effect of Changes in Rescue Medications for Breakthrough Emesis

The delayed phase antiemetic drugs for regimens B and C did not include a 5-HT_3RA for the base-case analysis. In the event of breakthrough emesis during the delayed phase, the base case analysis modeled the receipt of agents other than 5-HT_3RAs as rescue medications. A scenario analysis was conducted whereby the rescue medications for regimen B and regimen C included two doses of ondansetron 8 mg for two days in addition to the other rescue medications. The results obtained for this scenario are reported in Table 4-14.

The addition of 5-HT_3RA to rescue medications for regimen B increased the direct and total costs associated with regimen B, but did not have any impact on the dominance status or ICER of any other antiemetic regimens. The addition of 5-HT_3RA to rescue medications for regimen C increased the costs associated with regimen C and thus lead to a decrease in the ICER for regimen A to $3,043.64 and $2,698.79, from the payer and societal perspectives, respectively.

Effect of Changes in Indirect Costs Associated with CINV and its Treatment

The impact of variation in the average hourly wages on total costs, effectiveness and ICER of each antiemetic regimen from the societal perspective are presented in Table 4-15. Decreasing the average hourly wage by 20% resulted in an increase in the ICER of regimen A to $3,199.74 per patient with complete control of emesis, while increasing the average wage by 20% had little impact on the ICER of regimen A. There are uncertainties regarding the amount of lost productivity associated with delayed CINV. Thus, the number of hours of lost productivity were varied between 2.75 hours to 24 hours (equivalent to 3 work-days) to study its impact on the ICER of the antiemetic regimens. The results reported in Table 4-15 show that a decrease in the lost work hours to 2.75 increases the ICER to $3,314.70 per patient with complete control of emesis, while increasing the lost work hours to 24 hours decreases the ICER to $2,645.09.

Table 4-14: Change in the Antiemetic Regimen for Breakthrough Emesis for Highly Emetogenic Chemotherapy Model

		Parameter: Change in Rescue Medications in Delayed Phase for Regimen B			
Regimen	**Effectiveness**	**Direct Costs**	**ICER per patient with complete control of emesis**	**Total Costs**	**ICER per patient with complete control of emesis**
Regimen C	0.564	$187.05	-	$294.19	-
Regimen B	0.484	$336.20	Dominated[a]	$465.93	Dominated[a]
Regimen D	0.549	$389.99	Dominated[a]	$494.93	Dominated[a]
Regimen A	0.684	$593.25	$3,368.16	$659.37	$2,995.73
		Parameter: Change in Rescue Medications in Delayed Phase for Regimen C			
Regimen	**Effectiveness**	**Direct Costs**	**ICER per patient with complete control of emesis**	**Total Costs**	**ICER per patient with complete control of emesis**
Regimen C	0.564	$222.00	-	$328.78	-
Regimen B	0.484	$300.95	Dominated[a]	$431.20	Dominated[a]
Regimen D	0.549	$390.67	Dominated[a]	$494.89	Dominated[a]
Regimen A	0.684	$593.63	$3,043.64	$659.08	$2,689.79

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatment regimens compared to regimen C
[a] Dominated by regimen C

Table 4-15: Change in the Indirect Costs Associated with CINV and its Treatment for Highly Emetogenic Chemotherapy Model

		Total Costs				ICER per patient with complete control of emesis			
		Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Regimen A**	**Regimen B**	**Regimen C**	**Regimen D**
Base Case		$658.97	$431.56	$295.89	$494.84	$2,881.605	Dominated[a]	-	Dominated[a]
Parameter: Average Wage Per Hour									
	Range								
Average Wage	$14.96	$632.41	$376.92	$250.31	$451.35	$3,199.74	Dominated[a]	-	Dominated[a]
	$30.48	$672.82	$455.99	$315.70	$514.72	$2,990.58	Dominated[a]	-	Dominated[a]
Number of Hours of Lost Productivity									
	Range								
No. of Hours	2.75 hrs	$610.20	$333.47	$214.38	$416.51	$3,314.70	Dominated[a]	-	Dominated[a]
	24 hrs	$739.56	$586.59	$423.70	$619.41	$2,645.09	Dominated[a]	-	Dominated[a]

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatment regimens compared to regimen C
[a] Dominated by regimen C

Probabilistic Sensitivity Analysis for Highly Emetogenic Chemotherapy Model

Although, one-way sensitivity analyses are easy to understand, incremental costs and effectiveness do not depend on single parameters and the overall variability in the decision model cannot be captured completely. Probabilistic sensitivity analysis using second-order Monte Carlo simulation provides a method to simultaneously vary all the parameters to investigate the overall impact on ICERs. All costs and probabilities were given ranges and a triangular distribution was specified for each of the variable. Triangular distribution uses the lowest, highest and the most likely value of any parameter.

The results of the probabilistic sensitivity analysis from the payer and societal perspectives are presented in Table 4-16. Although the dominance status of the antiemetic regimens remained the same as in the base-case analysis, the ICER for regimen A increased to $3,923.51 per patient with complete protection from emesis from the payer perspective and increased to $3,524.75 per patient with complete protection from emesis from the societal perspective.

Table 4-16: Probabilistic Sensitivity Analysis for Costs, Effectiveness and Incremental Cost Effectiveness Ratios for Antiemetic Regimens for Prevention of CINV in Patients Receiving Highly Emetogenic Chemotherapy from a Payer Perspective

Treatment Strategy	**Side Effects Not Modeled**			
Payer Perspective	**Direct Costs Mean (SD)**	**Effectiveness Mean (SD)**	**Cost of achieveing one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen C (Metoclopramide)	$187.65 ($10.38)	0.561 (0.015)	$334.64	-
Regimen B (Standard)	$301.01 ($18.51)	0.482 (0.016)	$624.59	Dominated[a]
Regimen D (Ondansetron)	$386.74 ($18.83)	0.545 (0.047	$709.67	Dominated[a]
Regimen A (Aprepitant)	$594.28 ($25.91)	0.664 (0.031)	$894.47	$3,923.51

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatment regimens compared to regimen C
[a] Dominated by regimen C

Table 4-17: Probabilistic Sensitivity Analysis for Costs, Effectiveness and Incremental Cost Effectiveness Ratios for Antiemetic Regimens for Prevention of CINV in Patients Receiving Highly Emetogenic Chemotherapy from a Societal Perspective

Treatment Strategy	**Side Effects Not Modeled**			
Societal Perspective	**Total Costs Mean (SD)**	**Effectiveness Mean (SD)**	**Cost of achieveing one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen C (Metoclopramide)	$303.68 ($44.67)	0.560 (0.015)	$541.89	-
Regimen B (Standard)	$439.64 ($54.89)	0.482 (0.016)	$912.00	Dominated[a]
Regimen D (Ondansetron)	$499.28 ($48.73)	0.544 (0.046)	$917.67	Dominated[a]
Regimen A (Aprepitant)	$669.57 ($38.98)	0.664 (0.031)	$1,008.05	$3,524.75

Regimen A: Oral Aprepitant 125 mg + Oral Dexamethasone 12 mg + IV Ondansetron 32 mg (Day 1), Oral Aprepitant 80 mg (Days 2-3) + Oral Dexamethasone 8 mg (Days 2-4);
Regimen B: Oral Dexamethasone 20 mg + IV Ondansetron 32mg (Day 1), Oral Dexamethasone 8 mg BID (Days 2-4)
Regimen C: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Metoclopramide 20 mg QID (Days 2-4);
Regimen D: IV Dexamethasone 20 mg + IV Ondansetron 8 mg (Day 1), IM Dexamethasone 8mg BID (Days 2-3) and 4mg BID (Day 4) + Oral Ondansetron 8 mg BID (Days 2-4)
All treatment regimens compared to regimen C
[a] Dominated by regimen C

For Moderately Emetogenic Chemotherapy Decision Model – Base Case Analysis

Base Case Analysis Results

A decision model was constructed to evaluate the total costs and benefits of four prophylactic antiemetic regimens for prevention of CINV due to ME chemotherapy (Refer to Table 3-2). A hypothetical cohort of 10,000 cancer patients receiving ME chemotherapy was evaluated using first-order Monte Carlo simulation. The base case results for the costs, effectiveness, cost of achieving one patient with complete protection from emesis and the ICER for each of the four antiemetic regimens from the payer perspective are reported in Table 4-18.

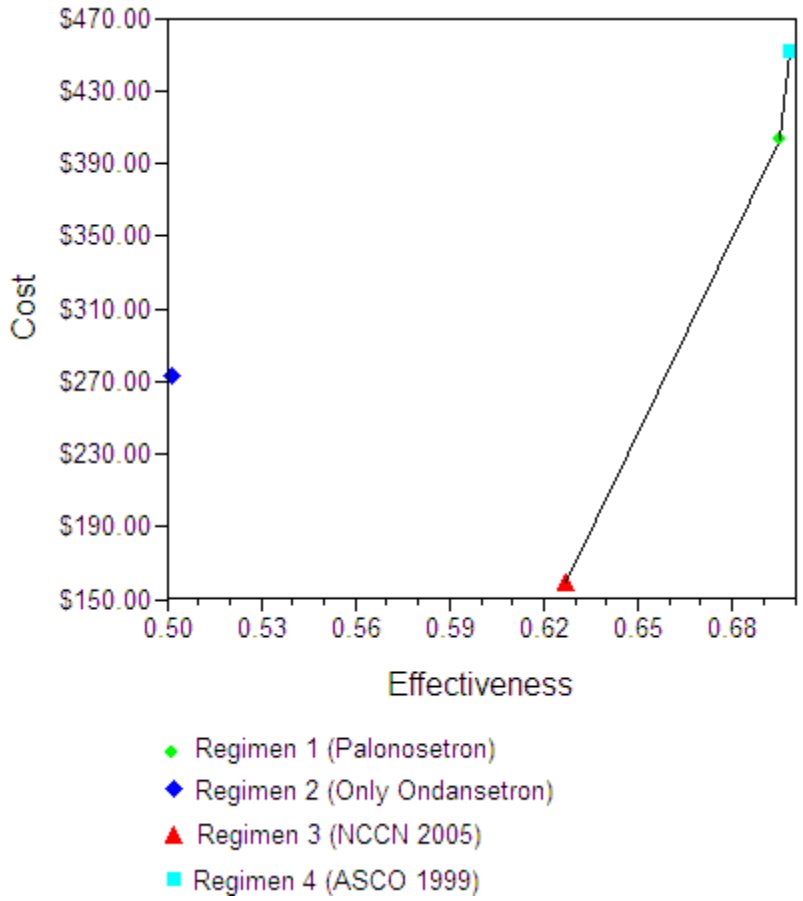
The results showed that regimen 3 was the least expensive while regimen 4 was the most costly prophylactic antiemetic regimen for prevention of CINV following ME chemotherapy. It was also evident from the results that the effectiveness estimates were equivalent for regimens 1 (regimen which includes palonosetron) and 4 (ASCO 1999 guidelines). The direct cost of achieving one patient with complete control of emesis with the regimen including palonosetron was approximately three times that of regimen 3. Under the base case assumptions, from the payer perspective, the ICER for regimen 1 over regimen 3 was $3,582.48 per patient with complete control of emesis. Regimen 2, with lower effectiveness and higher costs was dominated by regimen 3. The direct costs and effectiveness for the antiemetic regimens from the payer perspective are represented graphically in Figure 4-5.

Table 4-18: Base Case Results from Payer Perspective using Monte Carlo Simulation of 10,000 Patients with Cancer Receiving Moderately Emetogenic Chemotherapy

Treatment Strategy	Direct Costs Mean (SD)	Effectiveness Mean (SD)	Cost of achieveing one patient with complete control of emesis	Incremental cost effectiveness ratio/patient with complete control of emesis
Regimen 3 (NCCN)	$159.12 ($23.91)	0.627 (0.484)	$253.74	-
Regimen 2 (Only Ondansetron)	$273.08 ($34.63)	0.502 (0.500)	$544.09	Dominated*
Regimen 1 (Palonosetron)	$403.45 ($24.55)	0.695 (0.460)	$580.25	$3,582.48
Regimen 4 (ASCO)	$451.30 ($17.41)	0.699 (0.459)	$646.09	$14,953.27

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg;
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
* Regimen 2 was dominated by Regimen 3

Figure 4-5: Direct Costs, Effectiveness of Different Antiemetic Regimens for Patients Receiving Moderately Emetogenic Chemotherapy



Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

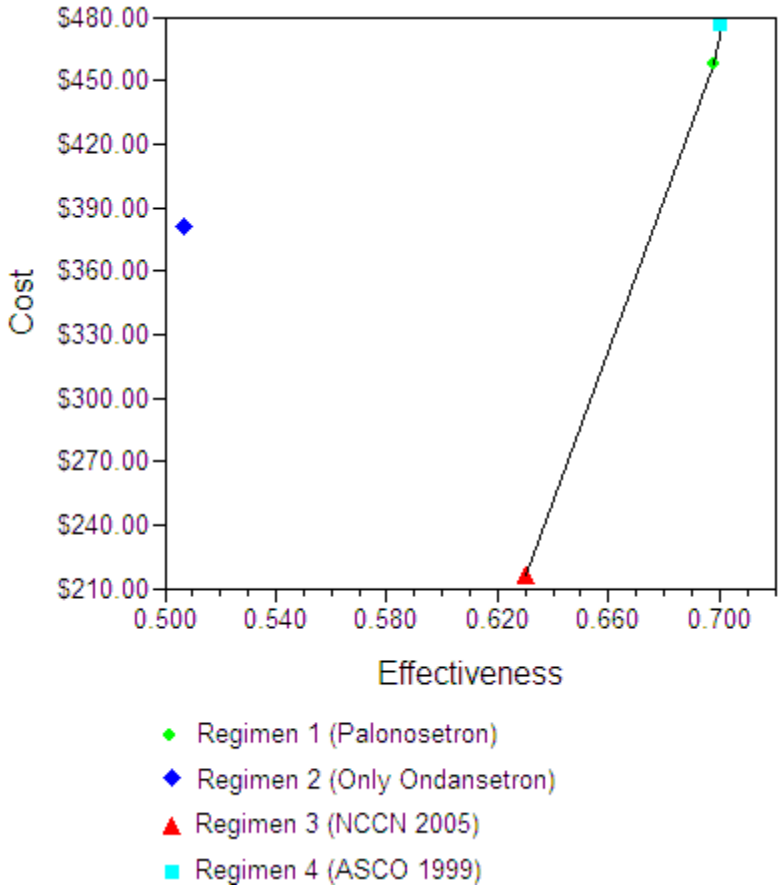
The base case results for the costs, effectiveness, cost of achieving one patient with complete protection from emesis and the ICER for each of the four antiemetic regimens from the societal perspective are reported in Table 4-19. The total costs and effectiveness for the antiemetic regimens from the societal perspective are represented graphically in Figure 4-6. Similar to the results from the payer perspective, regimen 2 was dominated by regimen 3. The mean costs for achieving one patient with complete control of emesis for each antiemetic regimen were higher compared to those obtained from the payer's perspective. The mean costs for achieving one patient with complete antiemetic protection for regimen 2 was higher ($752.03) as compared to regimen 1 ($655.65). From the societal perspective, the ICER for regimen 1 compared to regimen 3 was $3,549.02 per patient with complete control of emesis and for regimen 4 compared to regimen 1 was $6,499.87.

Table 4-19: Base Case Results from Payer Perspective using Monte Carlo Simulation of 10,000 Patients with Cancer Receiving Moderately Emetogenic Chemotherapy

Treatment Strategy	Total Costs Mean (SD)	Effectiveness Mean (SD)	Cost of achieveing one patient with complete control of emesis	Incremental cost effectiveness ratio/patient with complete control of emesis
Regimen 3 (NCCN)	$216.31 ($122.24)	0.630 (0.483)	$343.35	-
Regimen 2 (Only Ondansetron)	$381.05 ($149.06)	0.507 (0.500)	$752.03	Dominated*
Regimen 1 (Palonosetron)	$457.64 ($120.53)	0.698 (0.459)	$655.65	$3,549.02
Regimen 4 (ASCO)	$475.84 ($85.69)	0.701 (0.458)	$679.00	$6,499.87

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg;
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
* Regimen 2 was dominated by Regimen 3

Figure 4-6: Total Costs, Effectiveness of Different Antiemetic Regimens for Patients Receiving Moderately Emetogenic Chemotherapy



Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Sensitivity Analyses for Moderately Emetogenic Chemotherapy Model

Effect of Changes in Control of Acute and Delayed Emesis

The efficacy parameters, probability of no acute emesis, probability of no delayed emesis given no acute emesis and probability of no delayed emesis given acute emesis were varied over a plausible range obtained from published literature. Table 4-20 presents the range for sensitivity analysis and the direct costs and effectiveness from the payer's perspective. Table 4-21 presents the same results for the model from societal perspective. The ICER for each regimen obtained from sensitivity analyses are reported in Table 4-22.

The change in the probability of no acute emesis for regimen 1 had a significant impact on the costs, effectiveness and ICER of antiemetic regimens from the payer and societal perspectives. Decreasing the probability from 0.850 to 0.680 resulted in the regimen with palonosetron being dominated by regimen 3. Additionally, the ICER for regimen 4 was calculated in comparison to regimen 3, the only non-dominated option. This result was similar to the ICER of regimen 4 over regimen 3, calculated for base-case estimates (value not shown in the table). Conversely, increasing the probability of no acute emesis for regimen 1 from 0.850 to 0.900 changes the dominance status, with regimen 4 being dominated by regimen 3. The results were also sensitive to the variations in the probability of no acute emesis for regimens 3 and 4.

The changes in the probability of no delayed emesis given no acute emesis have a similar impact on the base-case results. Decreasing the probability for regimen 1 results in it being dominated by other regimens and increasing the probability, results in regimen 4 being dominated. Similarly, decreasing the probability for regimens 3 and 4 translates into higher costs and higher effectiveness of regimen 1, while increasing the probability of regimens 3 and 4 results in elimination of regimen 1 from ICER calculations based on dominance and extended dominance.

Table 4-20: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Efficacy Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Acute Emesis									
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Regimen	**Range**								
Regimen 1	0.680	$406.13	$273.10	$159.33	$451.39	0.554	0.503	0.625	0.696
	0.900	$402.84	$273.10	$159.33	$451.39	0.734	0.503	0.625	0.696
Regimen 2	0.576	$403.59	$275.00	$159.33	$451.39	0.693	0.402	0.625	0.696
	0.864	$403.59	$271.20	$159.33	$451.39	0.693	0.604	0.625	0.696
Regimen 3	0.714	$403.59	$273.10	$161.37	$452.99	0.693	0.503	0.500	0.557
	0.900	$403.59	$273.10	$159.23	$451.32	0.693	0.503	0.631	0.702
Regimen 4	0.714	$403.59	$273.10	$161.37	$452.99	0.693	0.503	0.500	0.557
	0.900	$403.59	$273.10	$159.23	$451.32	0.693	0.503	0.631	0.702

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-20 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Efficacy Parameters

Parameters/Range		**DIRECT COSTS**				**EFFECTIVENESS**			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Delayed Emesis Given No Acute Emesis									
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Regimen	**Range**								
Regimen 1	0.739	$405.95	$273.10	$159.33	$451.39	0.554	0.503	0.625	0.696
	0.950	$403.26	$273.10	$159.33	$451.39	0.713	0.503	0.625	0.696
Regimen 2	0.649	$403.59	$274.78	$159.33	$451.39	0.693	0.402	0.625	0.696
	0.950	$403.59	$271.69	$159.33	$451.39	0.693	0.589	0.625	0.696
Regimen 3	0.684	$403.59	$273.10	$161.56	$451.39	0.693	0.503	0.500	0.696
	0.950	$403.59	$273.10	$158.09	$451.39	0.693	0.503	0.694	0.696
Regimen 4	0.762	$403.59	$273.10	$159.33	$453.88	0.693	0.503	0.625	0.557
	1.000	$403.59	$273.10	$159.33	$450.77	0.693	0.503	0.625	0.731

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-20 (Continued): One Way Sensitivity Analyses Results For ME Model with No Side Effects from Payer Perspective– Efficacy Parameters

Parameters/Range		**DIRECT COSTS**				**EFFECTIVENESS**			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of No Delayed Emesis Given Acute Emesis									
Base Case		**$403.45**	**$273.08**	**$159.12**	**$451.30**	**0.695**	**0.502**	**0.627**	**0.699**
Regimen	**Range**								
Regimen 1	0.000	$403.89	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
	0.300	$403.21	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 2	0.000	$403.59	$273.53	$159.33	$451.39	0.693	0.503	0.625	0.696
	0.300	$403.59	$272.33	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 3	0.000	$403.59	$273.10	$159.80	$451.39	0.693	0.503	0.625	0.696
	0.568	$403.59	$273.10	$158.90	$451.39	0.693	0.503	0.625	0.696
Regimen 4	0.300	$403.59	$273.10	$159.33	$451.82	0.693	0.503	0.625	0.696
	0.682	$403.59	$273.10	$159.33	$451.21	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-21: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Efficacy Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Acute Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.680	$499.24	$382.14	$217.31	$476.71	0.554	0.503	0.625	0.696
	0.900	$446.72	$382.14	$217.31	$476.71	0.734	0.503	0.625	0.696
Regimen 2	0.576	$458.66	$412.76	$217.31	$476.71	0.693	0.402	0.625	0.696
	0.864	$458.66	$351.52	$217.31	$476.71	0.693	0.604	0.625	0.696
Regimen 3	0.714	$458.66	$382.14	$247.31	$497.65	0.693	0.503	0.500	0.557
	0.900	$458.66	$382.14	$215.96	$475.77	0.693	0.503	0.631	0.702
Regimen 4	0.714	$458.66	$382.14	$247.31	$497.65	0.693	0.503	0.500	0.557
	0.900	$458.66	$382.14	$215.96	$475.77	0.693	0.503	0.631	0.702

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-21 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Efficacy Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Delayed Emesis Given No Acute Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.739	$505.51	$382.14	$217.31	$476.71	0.554	0.503	0.625	0.696
	0.950	$452.08	$382.14	$217.31	$476.71	0.713	0.503	0.625	0.696
Regimen 2	0.649	$458.66	$417.02	$217.31	$476.71	0.693	0.402	0.625	0.696
	0.950	$458.66	$352.61	$217.31	$476.71	0.693	0.589	0.625	0.696
Regimen 3	0.684	$458.66	$382.14	$262.70	$476.71	0.693	0.503	0.500	0.696
	0.950	$458.66	$382.14	$192.09	$476.71	0.693	0.503	0.694	0.696
Regimen 4	0.762	$458.66	$382.14	$217.31	$527.14	0.693	0.503	0.625	0.557
	1.000	$458.66	$382.14	$217.31	$463.97	0.693	0.503	0.625	0.731

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-21 (Continued): One Way Sensitivity Analyses Results For ME Model with No Side Effects from Societal Perspective– Efficacy Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Delayed Emesis Given Acute Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.000	$464.60	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
	0.300	$451.20	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 2	0.000	$458.66	$391.04	$217.31	$476.71	0.693	0.503	0.625	0.696
	0.300	$458.66	$366.08	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 3	0.000	$458.66	$382.14	$226.95	$476.71	0.693	0.503	0.625	0.696
	0.568	$458.66	$382.14	$208.70	$476.71	0.693	0.503	0.625	0.696
Regimen 4	0.300	$458.66	$382.14	$217.31	$485.32	0.693	0.503	0.625	0.696
	0.682	$458.66	$382.14	$217.31	$473.04	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-22: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Efficacy Parameters

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Acute Emesis									
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Regimen	**Range**								
Regimen 1	0.680	Dominated[a]	Dominated[a]	-	$4,118.70	Dominated[a]	Dominated[a]	-	$3,658.01
	0.900	$2,237.88	Dominated[a]	-	Dominated[a]	$2,108.29	Dominated[a]	-	Dominated[a]
Regimen 2	0.576	$3,589.75	Dominated[a]	-	$16,655.68	$3,546.97	Dominated[a]	-	$6,292.08
	0.864	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
Regimen 3	0.714	$1,256.47	Extended Dominance[b]	-	Dominated[a]	$1,096.38	Extended Dominance[b]	-	Dominated[a]
	0.900	$3,913.53	Dominated[a]	-	$5,239.52	Extended Dominance[c]	Dominated[a]	-	$3,631.19
Regimen 4	0.714	$1,256.47	Extended Dominance[b]	-	Dominated[a]	$3,634.32	Dominated[a]	-	$4,220.16
	0.900	$3,913.53	Dominated[a]	-	$5,239.52	$3,437.29	Dominated[a]	-	$8,893.67

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens compared to regimen 3
[a] Dominated by regimen 3; [b] Dominated by a blend of regimen 3 and regimen 1; [c] Dominated by a blend of regimen 3 and 4

Table 4-22 (Continued): One Way Sensitivity Analyses Results For HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Efficacy Parameters

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of No Delayed Emesis Given No Acute Emesis									
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Regimen	**Range**								
Regimen 1	0.739	Dominated[a]	Dominated[a]	-	$4,118.70	Dominated[a]	Dominated[a]	-	$3,658.01
	0.950	$2,786.28	Dominated[a]	-	Dominated[a]	$2,681.61	Dominated[a]	-	Dominated[a]
Regimen 2	0.649	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	0.950	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
Regimen 3	0.684	$1,253.66	Extended Dominance[b]	-	$16,665.68	$1,015.05	Extended Dominance[b]	-	$6,292.08
	0.950	Dominated[a]	Dominated[a]	-	$200,606.36	Dominated[a]	Dominated[a]	-	$194,660.47
Regimen 4	0.762	$3,589.75	Dominated[a]	-	Dominated[a]	$3,546.97	Dominated[a]	-	Dominated[a]
	1.000	Extended Dominance[c]	Dominated[a]	-	$2,749.35	Extended Dominance[c]	Dominated[a]	-	$2,326.89

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens compared to regimen 3
[a] Dominated by regimen 3; [b] Dominated by a blend of regimen 3 and regimen 1; [c] Dominated by a blend of regimen 3 and 4

Table 4-22 (Continued): One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer and Societal Perspective – ICERs for Efficacy Parameters

		ICER – Payer Perspective				ICER – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of No Delayed Emesis Given Acute Emesis									
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Regimen	**Range**								
Regimen 1	0.000	$3,594.15	Dominated[a]	-	$16,561.40	$3,634.32	Dominated[a]	-	$4,220.16
	0.300	$3,584.23	Dominated[a]	-	$16,796.61	$3,437.29	Dominated[a]	-	$8,893.67
Regimen 2	0.000	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	0.300	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
Regimen 3	0.000	$,3582.77	Dominated[a]	-	$16,665.68	$3,405.27	Dominated[a]	-	$6,292.08
	0.568	$3,595.99	Dominated[a]	-	$16,665.68	$3,673.55	Dominated[a]	-	$6,292.08
Regimen 4	0.300	$3,589.75	Dominated[a]	-	$16,813.59	$3,546.97	Dominated[a]	-	$9,294.71
	0.682	$3,589.75	Dominated[a]	-	$16,602.76	$3,546.97	Dominated[a]	-	$5,014.84

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens are compared to regimen 3
[a] Dominated by regimen 3

Effect of Changes in the Receipt of Rescue Medications

The results of sensitivity analysis on the probability of receipt of rescue medications during acute and delayed phase are reported in Table 4-23 from the payer perspective and in Table 4-24 from the societal perspective. The ICER results are presented in Table 4-25. The results were not sensitive to changes in the probability of receiving rescue medications in the acute phase given acute emesis, and the probability of receiving rescue medications in the delayed phase given delayed emesis. The probabilities of receiving rescue medications in the acute phase given no acute emesis and in the delayed phase given no delayed emesis have a significant impact on the model results. For regimen 1, increasing the probability of receiving rescue medications in the acute phase given no acute emesis, and for regimens 3 and 4, decreasing the same probability resulted in a change in the dominance status of the various antiemetic regimens (Refer to Table 4-25). Similar changes were observed due to the variations in the probability of receiving rescue medications in the delayed phase given no delayed emesis for regimens 1, 3 and 4.

Effect of Changes in the Receipt of Outpatient Care

The results of sensitivity analysis on the probability of receipt of outpatient care during the acute and delayed phase from the payer perspective are reported in Tables 4-23 and 4-24. The ICER results are presented in Table 4-25. The base-case results were not sensitive to changes in the probability of receiving outpatient care either in the acute phase or the delayed phase. The dominance status of the antiemetic regimens remained the same as the base case results; from the payer and societal perspectives.

Table 4-23: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of Receiving Rescue Medications In the Acute Phase Given No Acute Emesis									
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Regimen	**Range**								
Regimen 1	0.000	$403.42	$273.10	$159.33	$451.39	0.727	0.503	0.625	0.696
	0.104	$403.69	$273.10	$159.33	$451.39	0.652	0.503	0.625	0.696
Regimen 2	0.000	$403.59	$273.05	$159.33	$451.39	0.693	0.528	0.625	0.696
	0.104	$403.59	$273.17	$159.33	$451.39	0.693	0.473	0.625	0.696
Regimen 3	0.000	$403.59	$273.10	$159.17	$451.24	0.693	0.503	0.698	0.777
	0.125	$403.59	$273.10	$159.36	$451.43	0.693	0.503	0.610	0.679
Regimen 4	0.000	$403.59	$273.10	$159.17	$451.24	0.693	0.503	0.698	0.777
	0.125	$403.59	$273.10	$159.36	$451.43	0.693	0.503	0.610	0.679

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-23 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given Acute Emesis									
Base Case									
Regimen	**Range**	$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Regimen 1	0.240	$403.57	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
	1.000	$403.76	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 2	0.240	$403.59	$273.01	$159.33	$451.39	0.693	0.503	0.625	0.696
	1.000	$403.59	$273.42	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 3	0.300	$403.59	$273.10	$159.29	$451.39	0.693	0.503	0.625	0.696
	1.000	$403.59	$273.10	$159.41	$451.39	0.693	0.503	0.625	0.696
Regimen 4	0.300	$403.59	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
	1.000	$403.59	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-23 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of Receiving Rescue Medications In the Delayed Phase Given No Delayed Emesis									
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Parameter	**Range**								
Regimen 1	0.000	$402.80	$273.10	$159.33	$451.39	0.749	0.503	0.625	0.696
	0.100	$403.87	$273.10	$159.33	$451.39	0.674	0.503	0.625	0.696
Regimen 2	0.000	$403.59	$272.32	$159.33	$451.39	0.693	0.557	0.625	0.696
	0.120	$403.59	$273.29	$159.33	$451.39	0.693	0.490	0.625	0.696
Regimen 3	0.000	$403.59	$273.10	$158.43	$451.39	0.693	0.503	0.683	0.696
	0.120	$403.59	$273.10	$159.69	$451.39	0.693	0.503	0.601	0.696
Regimen 4	0.000	$403.59	$273.10	$159.33	$450.37	0.693	0.503	0.625	0.761
	0.120	$403.59	$273.10	$159.33	$451.81	0.693	0.503	0.625	0.669

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-23 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Receipt of Rescue Medications

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of Receiving Rescue Medications In the Delayed Phase Given Delayed Emesis									
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Regimen	**Range**								
Regimen 1	0.400	$403.33	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
	1.000	$404.88	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 2	0.378	$403.59	$272.62	$159.33	$451.39	0.693	0.503	0.625	0.696
	1.000	$403.59	$275.79	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 3	0.389	$403.59	$273.10	$159.06	$451.39	0.693	0.503	0.625	0.696
	1.000	$403.59	$273.10	$160.72	$451.39	0.693	0.503	0.625	0.696
Regimen 4	0.389	$403.59	$273.10	$159.33	$451.28	0.693	0.503	0.625	0.696
	1.000	$403.59	$273.10	$159.33	$452.00	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-23 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Receipt of Outpatient Care

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		**$403.45**	**$273.08**	**$159.12**	**$451.30**	**0.695**	**0.502**	**0.627**	**0.699**
Parameter: Probability of Receipt of Outpatient Care During Acute Phase Given:									
No Rescue Medications	0.000	$403.31	$272.58	$159.19	$451.26	0.693	0.503	0.625	0.696
	0.030	$404.15	$274.15	$159.60	$451.67	0.693	0.503	0.625	0.696
Rescue Medications	0.000	$403.47	$272.88	$159.18	$451.24	0.693	0.503	0.625	0.696
	0.030	$403.83	$273.55	$159.63	$451.70	0.693	0.503	0.625	0.696
Parameter: Probability of Receipt of Outpatient Care During Delayed Phase Given:									
No Rescue Medications	0.02	$403.20	$272.28	$158.90	$451.21	0.693	0.503	0.625	0.696
	0.05	$403.98	$273.92	$159.75	$451.58	0.693	0.503	0.625	0.696
Rescue Medications	0.02	$403.20	$272.37	$158.93	$451.22	0.693	0.503	0.625	0.696
	0.05	$403.98	$273.83	$159.73	$451.57	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-24: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given No Acute Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.000	$458.59	$382.14	$217.31	$476.71	0.727	0.503	0.625	0.696
	0.104	$458.74	$382.14	$217.31	$476.71	0.652	0.503	0.625	0.696
Regimen 2	0.000	$458.66	$382.08	$217.31	$476.71	0.693	0.528	0.625	0.696
	0.104	$458.66	$382.21	$217.31	$476.71	0.693	0.473	0.625	0.696
Regimen 3	0.000	$458.66	$382.14	$217.16	$476.56	0.693	0.503	0.698	0.777
	0.125	$458.66	$382.14	$217.34	$476.74	0.693	0.503	0.610	0.679
Regimen 4	0.000	$458.66	$382.14	$217.16	$476.56	0.693	0.503	0.698	0.777
	0.125	$458.66	$382.14	$217.34	$476.74	0.693	0.503	0.610	0.679

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-24 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given Acute Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.240	$458.64	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
	1.000	$458.83	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 2	0.240	$458.66	$382.11	$217.31	$476.71	0.693	0.503	0.625	0.696
	1.000	$458.66	$382.46	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 3	0.300	$458.66	$382.14	$217.27	$476.67	0.693	0.503	0.625	0.696
	1.000	$458.66	$382.14	$217.39	$476.79	0.693	0.503	0.625	0.696
Regimen 4	0.300	$458.66	$382.14	$217.39	$476.79	0.693	0.503	0.625	0.696
	1.000	$458.66	$382.14	$217.39	$476.79	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-24 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Probability of Receiving Rescue Medications In the Delayed Phase Given No Delayed Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.000	$457.87	$382.14	$217.31	$476.71	0.749	0.503	0.625	0.696
	0.100	$458.94	$382.14	$217.31	$476.71	0.674	0.503	0.625	0.696
Regimen 2	0.000	$458.66	$381.35	$217.31	$476.71	0.693	0.557	0.625	0.696
	0.120	$458.66	$382.33	$217.31	$476.71	0.693	0.490	0.625	0.696
Regimen 3	0.000	$458.66	$382.14	$216.41	$476.71	0.693	0.503	0.683	0.696
	0.120	$458.66	$382.14	$217.67	$476.71	0.693	0.503	0.601	0.696
Regimen 4	0.000	$458.66	$382.14	$217.31	$475.68	0.693	0.503	0.625	0.761
	0.120	$458.66	$382.14	$217.31	$477.13	0.693	0.503	0.625	0.669

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-24 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Receipt of Rescue Medications

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of Receiving Rescue Medications In the Delayed Phase Given Delayed Emesis									
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Regimen	**Range**								
Regimen 1	0.400	$458.40	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
	1.000	$459.95	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 2	0.378	$458.66	$381.66	$217.31	$476.71	0.693	0.503	0.625	0.696
	1.000	$458.66	$384.83	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 3	0.389	$458.66	$382.14	$217.05	$476.71	0.693	0.503	0.625	0.696
	1.000	$458.66	$382.14	$218.70	$476.71	0.693	0.503	0.625	0.696
Regimen 4	0.389	$458.66	$382.14	$217.31	$476.59	0.693	0.503	0.625	0.696
	1.000	$458.66	$382.14	$217.31	$477.32	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-24 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Receipt of Outpatient Care

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Parameter: Probability of Receipt of Outpatient Care During Acute Phase Given:									
No Rescue Medications	0.000	$458.38	$381.62	$217.17	$476.57	0.693	0.503	0.625	0.696
	0.030	$459.22	$383.19	$217.58	$476.98	0.693	0.503	0.625	0.696
Rescue Medications	0.000	$458.54	$381.91	$217.16	$476.56	0.693	0.503	0.625	0.696
	0.030	$458.90	$382.59	$217.61	$477.01	0.693	0.503	0.625	0.696
Probability of Receipt of Outpatient Care During Delayed Phase Given:									
No Rescue Medications	0.02	$458.27	$381.32	$216.89	$476.52	0.693	0.503	0.625	0.696
	0.05	$459.05	$382.96	$217.73	$476.89	0.693	0.503	0.625	0.696
Rescue Medications	0.02	$458.27	$381.41	$216.91	$476.53	0.693	0.503	0.625	0.696
	0.05	$459.05	$382.87	$217.71	$476.88	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-25: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Parameter: Probability of Receiving Rescue Medications In the Acute Phase Given No Acute Emesis									
Regimen 1	0.000	$2,388.78	Dominated[a]	-	Dominated[a]	$2,360.30	Dominated[a]	-	Dominated
	0.104	Extended Dominance[b]	Dominated[a]	-	$4,118.69	Extended Dominance[b]	Dominated[a]	-	$3,658.01
Regimen 2	0.000	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	0.104	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]		$6,292.08
Regimen 3	0.000	Dominated[a]	Dominated[a]	-	$3,690.35	Dominated[a]	Dominated[a]	-	$3,277.58
	0.125	$2,953.43	Dominated[a]	-	Dominated[a]	$2,918.23	Dominated[a]	-	Dominated
Regimen 4	0.000	Dominated[a]	Dominated[a]	-	$3,690.35	Dominated[a]	Dominated[a]	-	$3,277.58
	0.125	$2,953.43	Dominated[a]	-	Dominated[a]	$2,918.23	Dominated[a]	-	Dominated

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3
[a] Dominated by regimen 3
[b] Dominated by a blend of regimen 3 and regimen 4

Table 4-25 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of Receiving Rescue Medications In the Acute Phase Given Acute Emesis									
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Regimen	**Range**								
Regimen 1	0.240	$3,589.54	Dominated[a]	-	$16,670.84	$3,546.75	Dominated[a]	-	$6,297.24
	1.000	$3,592.29	Dominated[a]	-	$16,605.50	$3,549.51	Dominated[a]	-	$6,231.90
Regimen 2	0.240	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	1.000	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
Regimen 3	0.300	$3,590.34	Dominated[a]	-	$16,651.87	$3,547.55	Dominated[a]	-	$6,278.28
	1.000	$3,588.51	Dominated[a]	-	$16,695.20	$3,545.72	Dominated[a]	-	$6,321.61
Regimen 4	0.300	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	1.000	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3
[a] Dominated by regimen 3

Table 4-25 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of Receiving Rescue Medications In the Delayed Phase Given No Delayed Emesis									
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Regimen	**Range**								
Regimen A	0.000	$1,972.53	Dominated[a]	-	Dominated[a]	$1,948.94	Dominated[a]	-	Dominated[a]
	0.100	Extended Dominance[b]	Dominated[a]	-	$4,118.70	Extended Dominance[b]	Dominated[a]	-	$3,658.01
Regimen B	0.000	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	0.120	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
Regimen C	0.000	Extended Dominance[b]	Dominated[a]	-	$23,208.07	Extended Dominance[b]	Dominated[a]	-	$20,620.16
	0.120	$2,658.10	Dominated[a]	-	$16,665.68	$2,626.37	Dominated[a]	-	$6,292.08
Regimen D	0.000	Dominated[a]	Dominated[a]	-	$2,412.92	Extended Dominance[b]	Dominated[a]	-	$1,902.38
	0.120	$3,589.75	Dominated[a]	-	Dominated[a]	$,3546.97	Dominated[a]	-	Dominated[a]

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3
[a] Dominated by regimen 3
[b] Dominated by a blend of regimens 3 and 4

Table 4-25 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Rescue Medications

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Probability of Receiving Rescue Medications In the Delayed Phase Given Delayed Emesis									
Base Case		$3,582.48	Dominated	-	$14,953.27	$3,549.02	Dominated	-	$6,499.87
Regimen	**Range**								
Regimen A	0.400	$3,585.97	Dominated	-	$16,755.44	$3,543.19	Dominated	-	$6,381.85
	1.000	$3,608.68	Dominated	-	$16,216.85	$3,565.89	Dominated	-	$5,843.26
Regimen B	0.378	$3,589.75	Dominated	-	$16,665.68	$3,546.97	Dominated	-	$6,292.08
	1.000	$3,589.75	Dominated	-	$16,665.68	$3,546.97	Dominated	-	$6,292.08
Regimen C	0.389	$3,593.62	Dominated	-	$16,665.68	$3,550.83	Dominated	-	$6,292.08
	1.000	$3,569.27	Dominated	-	$16,665.68	$3,526.49	Dominated	-	$6,292.08
Regimen D	0.389	$3,589.75	Dominated	-	$16,625.65	$3,546.97	Dominated	-	$6,252.06
	1.000	$3,589.75	Dominated	-	$16,877.76	$3,546.97	Dominated	-	$6,504.16

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3
[a] Dominated by regimen 3

Table 4-25 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Receipt of Outpatient Care

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated[a]	-	$6,499.87
Parameter: Probability of Receipt of Outpatient Care During Acute Phase Given:									
No Rescue Medications	0.000	$3,587.65	Dominated[a]	-	$16,715.53	$3,544.87	Dominated[a]	-	$6,341.93
	0.030	$3,593.96	Dominated[a]	-	$16,565.97	$3,551.17	Dominated[a]	-	$6,192.38
Rescue Medications	0.000	$3,590.21	Dominated[a]	-	$16,654.97	$3,547.42	Dominated[a]	-	$6,281.38
	0.030	$3,588.85	Dominated[a]	-	$16,687.09	$3,546.07	Dominated[a]	-	$6,313.49
Parameter: Probability of Receipt of Outpatient Care During Delayed Phase Given:									
No Rescue Medications	0.020	$3,590.23	Dominated[a]	-	$16,737.45	$3,546.73	Dominated[a]	-	$6,256.19
	0.050	$3,589.28	Dominated[a]	-	$16,593.90	$3,546.73	Dominated[a]	-	$6,220.31
Rescue Medications	0.020	$3,589.89	Dominated[a]	-	$16,740.96	$3,547.10	Dominated[a]	-	$6,367.36
	0.050	$3,589.62	Dominated[a]	-	$16,590.40	$3,546.83	Dominated[a]	-	$6,216.80

Regimen 1: IV Palonosetron 0.25mg; **Regimen 2**: IV Ondansetron 32mg, **Regimen 3**: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5); **Regimen 4**: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3; [a] Dominated by regimen 3

Effect of Changes in the Cost and Utilization Parameters

The impact of changes in the total cost of prophylactic antiemetic regimens, cost of palonosetron, cost of ondansetron, infusion costs, and the number of days of receiving rescue medications during the delayed phase from the payer and societal perspectives are reported in Tables 4-26 and 4-27, respectively. The ICER results are presented in Table 4-28. The ICER results showed that regimen 1 was dominated by regimen 3 for four conditions, 1) when the cost of regimen 1 was increased by 20%, 2) decreasing the cost of regimen 4 by 20%, 3) increasing the cost of palonosetron by 20%, and 4) decreasing the cost of ondansetron by 20%.

Effect of Changes in Rescue Medications for Breakthrough Emesis

The delayed phase antiemetic regimen for strategies 1, 2 and 3 did not include a 5-HT_3RA in the base-case analysis. In the event of breakthrough emesis in the delayed phase, prochlorperazine was the rescue medication used for base-case analysis. The use of 5-HT_3RA if not used prophylactically, is recommended by some guidelines. A scenario analysis was conducted in which rescue medications for regimens 1, 2 and 3 included two doses of ondansetron 8 mg for two days in addition to the other rescue medications. The impact of changes in rescue medications for breakthrough emesis during delayed phase on costs and ICERs are reported in Table 4-29.

Addition of ondansetron as rescue medication in the delayed phase changed the dominance status of the antiemetic regimens from the societal perspective. Regimen 1 was dominated by regimen 4 and the ICER for regimen 4 over regimen 3 was $3,658.01 per patient with complete control of emesis. The change in the rescue medications in the delayed phase for regimen 2 did not change the dominance status and the ICER of the antiemetic regimens. The results were sensitive to the changes made for regimen 3. Although the dominance status remained same, the total costs for regimen 3 increased resulting in a decrease in the ICER of regimen A.

Table 4-26: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Payer Perspective – Cost Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Parameter: Total Prophylactic Antiemetic Regimen Costs									
Regimen	**Range**								
Regimen 1	$319.31	$323.75	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
	$478.98	$483.42	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 2	$212.29	$403.59	$220.03	$159.33	$451.39	0.693	0.503	0.625	0.696
	$318.43	$403.59	$326.17	$159.33	$451.39	0.693	0.503	0.625	0.696
Regimen 3	$123.73	$403.59	$273.10	$128.40	$451.39	0.693	0.503	0.625	0.696
	$185.59	$403.59	$273.10	$190.26	$451.39	0.693	0.503	0.625	0.696
Regimen 4	$358.74	$403.59	$273.10	$159.33	$361.71	0.693	0.503	0.625	0.696
	$538.10	$403.59	$273.10	$159.33	$541.07	0.693	0.503	0.625	0.696
Cost of Palonosetron									
Palonosetron	$272.16	$335.55	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696
	$408.24	$471.63	$273.10	$159.33	$451.39	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-26 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer Perspective – Cost Parameters

		DIRECT COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$403.45	$273.08	$159.12	$451.30	0.695	0.502	0.627	0.699
Parameter: Cost of IV Ondansetron									
Ondansetron	$165.13	$403.59	$231.70	$149.00	$382.40	0.693	0.503	0.625	0.696
	$247.69	$403.70	$314.50	$169.70	$520.40	0.693	0.503	0.625	0.696
Parameter: Infusion Costs									
First Drug	$47.16	$391.70	$261.12	$147.44	$439.55	0.693	0.503	0.625	0.696
	$70.74	$415.48	$285.08	$171.21	$463.23	0.693	0.503	0.625	0.696
Second Drug	$22.18	$403.59	$273.10	$153.79	$445.85	0.693	0.503	0.625	0.696
	$33.26	$403.59	$273.10	$273.10	$456.93	0.693	0.503	0.625	0.696
Parameter: Number of Days of Receiving Rescue Medications During Delayed Phase									
No. of Days	1 day	$403.07	$272.31	$158.78	$450.99	0.693	0.503	0.625	0.696
	3 days	$404.10	$273.89	$159.88	$451.79	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-27: One Way Sensitivity Analyses Results for HE Model with No Side Effects from Societal Perspective – Cost Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Parameter: Total Prophylactic Antiemetic Regimen Costs									
Regimen	**Range**								
Regimen 1	$319.31	$378.82	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
	$478.98	$538.49	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 2	$212.29	$458.66	$329.07	$217.31	$476.71	0.693	0.503	0.625	0.696
	$318.43	$458.66	$435.21	$217.31	$476.71	0.693	0.503	0.625	0.696
Regimen 3	$123.73	$458.66	$382.14	$186.38	$476.71	0.693	0.503	0.625	0.696
	$185.59	$458.66	$382.14	$248.24	$476.71	0.693	0.503	0.625	0.696
Regimen 4	$358.74	$458.66	$382.14	$217.31	$387.03	0.693	0.503	0.625	0.696
	$538.10	$458.66	$382.14	$217.31	$566.39	0.693	0.503	0.625	0.696
Parameter: Cost of Palonosetron									
Palonosetron	$272.16	$390.62	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696
	$408.24	$526.70	$382.14	$217.31	$476.71	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-27 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Societal Perspective – Cost Parameters

		TOTAL COSTS				EFFECTIVENESS			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$457.64	$381.05	$216.31	$475.84	0.698	0.500	0.630	0.701
Parameter: Cost of IV Ondansetron									
Ondansetron	$165.13	$458.66	$340.70	$207.00	$407.70	0.693	0.503	0.625	0.696
	$247.69	$458.66	$423.60	$227.70	$545.70	0.693	0.503	0.625	0.696
Parameter: Infusion Costs									
First Drug	$47.16	$446.77	$370.16	$205.42	$464.87	0.693	0.503	0.625	0.696
	$70.74	$470.55	$394.12	$229.20	$488.55	0.693	0.503	0.625	0.696
Second Drug	$22.18	$458.66	$382.14	$211.77	$471.17	0.693	0.503	0.625	0.696
	$33.26	$458.66	$382.14	$222.85	$482.25	0.693	0.503	0.625	0.696
Parameter: Number of Days of Receiving Rescue Medications During Delayed Phase									
No. of Days	1 day	$458.14	$381.35	$216.76	$476.31	0.693	0.503	0.625	0.696
	3 days	$459.17	$382.93	$217.86	$477.11	0.693	0.503	0.625	0.696

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

Table 4-28: One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Cost and Utilization Parameters

		ICER per patient with complete control of emesis – Payer Perspective				ICER per patient with complete control of emesis – Societal Perspective			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Parameter: Total Costs of Prophylactic Antiemetic Regimens									
Base Case		$3,582.48	Dominated	-	$14,953.27	$3,549.02	Dominated [a]	-	$6,499.87
Regimen	**Range**								
Regimen 1	$319.31	$2,416.40	Dominated[a]	-	$44,498.76	$2,373.61	Dominated[a]	-	$34,125.16
	$478.98	Dominated[a]	Dominated[a]	-	$4,118.70	Dominated [a]	Dominated[a]	-	$3,658.01
Regimen 2	$212.29	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
	$318.43	$3,589.75	Dominated[a]	-	$16,665.68	$3,546.97	Dominated[a]	-	$6,292.08
Regimen 3	$123.73	$4,044.31	Dominated[a]	-	$16,665.68	$4,001.53	Dominated[a]	-	$6,292.08
	$185.59	$3,135.20	Dominated[a]	-	$16,665.68	$3,092.41	Dominated[a]	-	$6,292.08
Regimen 4	$358.74	Dominated[a]	Dominated[a]	-	$2,854.04	Dominated [a]	Dominated[a]	-	$2,393.36
	$538.10	$3,589.75	Dominated[a]	-	$47,929.09	$3,546.97	Dominated[a]	-	$37,555.49
Parameter: Cost of Palonosetron									
Palonosetron	$272.16	$2,589.81	Dominated[a]	-	$40,385.15	$2,547.03	Dominated[a]	-	$30,011.56
	$408.24	Dominated[a]	Dominated[a]	-	$4,118.70	Dominated [a]	Dominated[a]	-	$3,658.01

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3; [a] Dominated by regimen 3

Table 4-28 (Continued): One Way Sensitivity Analyses Results for ME Model with No Side Effects from Payer and Societal Perspective – ICERs for Cost and Utilization Parameters

Parameters/Range		**ICER per patient with complete control of emesis – Payer Perspective**				**ICER per patient with complete control of emesis – Societal Perspective**			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$3,582.48	Dominated[a]	-	$14,953.27	$3,549.02	Dominated [a]	-	$6,499.87
Parameter: Cost of IV Ondansetron									
Ondansetron	$165.13	Dominated	Dominated[a]	-	$3,291.22	Dominated	Dominated[a]	-	$2,830.54
	$247.69	$3,438.98	Dominated[a]	-	$40,698.18	$3,396.19	Dominated[a]	-	$30,324.58
Infusion Costs									
First Drug	$47.16	$,3589.74	Dominated[a]	-	$16,682.53	$3,546.96	Dominated[a]	-	$6,308.94
	$70.74	$3,589.76	Dominated[a]	-	$16,648.82	$3,546.96	Dominated[a]	-	$6,275.22
Second Drug	$22.18	$3,671.17	Dominated[a]	-	$14,734.37	$3,628.39	Dominated[a]	-	$4,360.78
	$33.26	$3,508.33	Dominated[a]	-	$18,596.98	$3,465.55	Dominated[a]	-	$8,233.38
Parameter: Number of Days of Receiving Rescue Medications During Delayed Phase									
No. of Days	1 day	$3,590.26	Dominated[a]	-	$16,706.68	$3,547.48	Dominated[a]	-	$6,333.08
	3 days	$3,589.25	Dominated[a]	-	$16,624.68	$3,546.46	Dominated[a]	-	$6,251.08

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3
[a] Dominated by regimen 3

Table 4-29: Change in the Antiemetic Regimen for Breakthrough Emesis

			Change in Rescue Meds in Delayed Phase for Regimen 1		
Regimen	**Effectiveness**	**Direct Costs**	**ICER per patient with complete control of emesis**	**Total Costs**	**ICER per patient with complete control of emesis**
Regimen 3	0.627	$159.33	-	$217.31	-
Regimen 2	0.502	$273.10	Dominated by regimen 3	$382.14	Dominated by regimen 3
Regimen 1	0.693	$425.60	$3,913.32	$480.68	Dominated by regimen 4
Regimen 4	0.696	$451.39	$8,990.44	$476.71	$3,658.01
			Change in Rescue Meds in Delayed Phase for Regimen 2		
Regimen	**Effectiveness**	**Direct Costs**	**ICER per patient with complete control of emesis**	**Total Costs**	**ICER per patient with complete control of emesis**
Regimen 3	0.627	$159.33	-	$182.80	-
Regimen 2	0.502	$306.96	Dominated by regimen 3	$273.10	Dominated by regimen 3
Regimen 1	0.693	$403.50	$3,589.75	$403.50	$3,244.54
Regimen 4	0.696	$451.39	$16,665.68	$451.39	$16,665.68
			Change in Rescue Meds in Delayed Phase for Regimen 3		
Regimen	**Effectiveness**	**Direct Costs**	**ICER per patient with complete control of emesis**	**Total Costs**	**ICER per patient with complete control of emesis**
Regimen 3	0.627	$182.80	-	$240.80	-
Regimen 2	0.502	$273.10	Dominated by regimen 3	$382.14	Dominated by regimen 3
Regimen 1	0.693	$403.50	$3,244.54	$458.56	$3,201.76
Regimen 4	0.696	$451.39	$16,665.68	$476.71	$6,292.08

Effect of Changes in Indirect Costs Associated with CINV and its Treatment

The impact of variation in the average hourly wages on total costs, effectiveness, and ICER for each antiemetic regimen from the societal perspective is presented in Table 4-30. Decreasing the hourly wage by 20% resulted in an increase in the ICER of regimen 4 from $6,499.87 to $10,631.89 per patient with complete control of emesis. Due to lack of sufficient and reliable data regarding the amount of lost productivity associated with delayed CINV, it was varied in sensitivity analysis to understand its impact on costs and ICERs. Decreasing the number of hours of lost productivity to 2.75 hours increased the ICER of regimen 4 to $14,072.28 per patient with complete control of emesis, while increasing the number of hours of lost productivity to 24 hours (equivalent to 3 work-days) decreased the ICER of regimen 4 to $3,113.57.

Table 4-30: Change in the Indirect Costs Associated with CINV and its Treatment

		TOTAL COSTS				ICER per patient with complete control of emesis			
		Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 1**	**Regimen 2**	**Regimen 3**	**Regimen 4**
Base Case		$457.64	$381.05	$216.31	$475.84	$3,549.02	Dominated [a]	-	$6,499.87
Parameter: Average Wage Per Hour									
Average Wage	$14.96	$435.62	$336.52	$193.05	$466.12	$3,564.87	Dominated [a]	-	$10,631.89
	$30.48	$468.85	$402.32	$228.04	$481.39	$3,539.05	Dominated [a]	-	$4,372.24
Parameter: Number of Hours of Lost Productivity									
No. of Hours	2.75 hrs	$417.36	$300.36	$173.82	$457.72	$3,579.06	Dominated [a]	-	$14,072.28
	24 hrs	$523.74	$511.00	$285.83	$506.62	Dominated [a]	Dominated [a]	-	$3,113.57

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3
[a] Dominated by regimen 3

Probabilistic Sensitivity Analysis for Moderately Emetogenic Chemotherapy Model

The results of probabilistic sensitivity analysis from the payer perspectives are shown in Table 4-31. The results were very sensitive to the simultaneous variation in all the parameters. From the payer perspective, regimen 2 was dominated by regimen 3 while regimen 1 was excluded from the ICER calculations due to extended dominance. The ICER of regimen 4 compared to regimen 1 was $3,091.58 per patient with complete control of emesis and compared to regimen 3 was calculated to be $5,370.87 per patient with complete control of emesis. The results of probabilistic sensitivity analysis from the societal perspectives are shown in Table 4-32. The results for the societal perspective were similar to those for the payer perspective. From the societal perspective, the ICER of regimen 4 compared to regimen 1 was $1,446.30 per patient with complete control of emesis and compared to regimen 3 was $4,831.22 per patient with complete control of emesis.

Table 4-31: Probabilistic Sensitivity Analysis for Costs, Effectiveness and Incremental Cost Effectiveness Ratios for Antiemetic Regimens for Prevention of CINV in Patients Receiving Highly Emetogenic Chemotherapy from a Payer Perspective

Treatment Strategy	Payer Perspective			
	Direct Costs Mean (SD)	**Effectiveness Mean (SD)**	**Cost of achieveing one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen 3	$179.21 (8.24)	0.596 (0.056)	$300.65	-
Regimen 2	$279.86 (17.72)	0.510 (0.060)	$549.04	Dominated*
Regimen 1	$411.05 (28.33)	0.631 (0.054)	$651.45	Extended Dominance**
Regimen 4	$471.24 (25.31)	0.651 (0.056)	$724.49	$3,091.58¶

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)
All regimens were compared to regimen 3

* Regimen 2 was dominated by regimen 3
** Regimen 1 is dominated by a blend of regimen 3 and regimen 4 with a coefficient of inequity between 0.206 and 0.358
¶ ICER for regimen 4 compared to regimen 3 without excluding the extended dominance strategy

Table 4-32: Probabilistic Sensitivity Analysis for Costs, Effectiveness and Incremental Cost Effectiveness Ratios for Antiemetic Regimens for Prevention of CINV in Patients Receiving Highly Emetogenic Chemotherapy from a Societal Perspective

Treatment Strategy	Societal Perspective			
	Total Costs Mean (SD)	**Effectiveness Mean (SD)**	**Cost of achieveing one patient with complete control of emesis**	**Incremental cost effectiveness ratio/patient with complete control of emesis**
Regimen 3	$256.49 (35.31)	0.596 (0.056)	$430.01	-
Regimen 2	$394.30 (51.12)	0.510 (0.061)	$773.31	Dominated[*]
Regimen 1	$490.85 (44.84)	0.631 (0.054)	$777.30	Extended Dominance[a]
Regimen 4	$518.72 (34.82)	0.651 (0.056)	$797.10	$1,446.30[¶]

Regimen 1: IV Palonosetron 0.25mg;
Regimen 2: IV Ondansetron 32mg,
Regimen 3: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5);
Regimen 4: IV Ondansetron 8mg + IV Dexamethasone 8mg, Oral Dexamethasone 4mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)

All regimens were compared to regimen 3
[*] Regimen 2 was dominated by regimen 3
[¶] ICER for regimen 4 compared to regimen 3 without excluding the extended dominance strategy
[a] Regimen 1 is dominated by a blend of regimen 3 and regimen 4 with a coefficient of inequity between 0.106 and 0.355

4.2: Results for Phase II

Phase II of this study involved face-to-face interviews of cancer patients to determine their willingness-to-pay for improved emesis control due to two new antiemetic regimens for prevention of CINV. The WTP amounts were then used as a measure of benefits to conduct cost-benefit analyses of new antiemetic agents for prevention of CINV due to highly emetogenic and moderately emetogenic chemotherapy agents.

A total of 124 patients with cancer were approached by nurses or oncologists for participation in the study. Out of 124 patients, four patients refused to participate in the study. A total of 120 patients agreed to participate in the study yielding a response rate of 96.8%. Of the 120 respondents, 59 respondents received version A and 61 received version B of the survey.

Demographic Characteristics of Study Participants

As shown in Table 4-33, the mean age of the study population was 56.5 years (SD = 12.0 years, range = 22 – 85 years). Sixty percent of the study population was female. More than 44% of the study population had annual household income level below $30,000. Approximately 58% of the respondents had one more member in their household and 13% of the respondents lived alone. Approximately 39% of respondents had primary health care coverage through their or their spouse's employer. Almost 36% of the respondents had Medicare as their primary health care insurer.

Table 4-33: Demographic Characteristics of Respondents

Demographic Characteristics	N (Valid %) Total N = 120
Age - Mean (SD)	56.5 (12.0)
Gender	
Male	48 (40.0%)
Female	72 (60.0%)
Race	
White	117 (97.5%)
African American	2 (1.7%)
Asian	1 (0.8%)
Education Level	
Less than high school education	22 (18.3%)
Completed high school education	53 (44.2%)
More than high school education	45 (37.5%)
Marital Status	
Married	93 (77.5%)
Not Married/Single/Divorced/Widowed	27 (22.5%)
Employment	
Not working	88 (73.3%)
Working (Part-time or Full-time)	32 (26.7%)
Annual Household Income Level	
≤$30,000	53 (44.2%)
$30,001 - $60,000	37 (30.8%)
>$60,000	30 (25.0%)
Type of Primary Insurance	
Medicare	43 (35.8%)
Medicaid	15 (12.5%)
Employer-based	47 (39.2%)
No coverage	5 (4.2%)
Other[a]	10 (8.3%)

[a] Other type of insurance coverage included self coverage, VA, MAMSI

Clinical Characteristics of Study Participants

Table 4-34 shows the clinical characteristics of all the respondents. With 28% of patients diagnosed with breast cancer, it was the most prevalent type of cancer among the study population followed by lung cancer (23.3% of respondents). Based on the algorithm for classifying combination chemotherapy regimens as defined in Tables 2-3 and 2-4 in Chapter 2, almost 57% of the respondents received highly emetogenic chemotherapy. Only 10% of all respondents received cisplatin-based highly emetogenic chemotherapy. All study participants had received prophylactic antiemetic regimens before chemotherapy for prevention of CINV during the acute phase. A majority of the study respondents (54.2%) received a combination of a 5-HT_3RA and corticosteroid before chemotherapy. With 16.7% of respondents, the combination of Aloxi and a corticosteroid was the next most common antiemetic regimen prescribed. The three-drug regimen of aprepitant (Emend®), 5-HT_3RA and corticosteroid was prescribed to approximately 8% of the patients. Ten percent of the patients received a single drug regimen of 5-HT_3RA. The study results also showed that various other antiemetic combination regimens such as Aloxi+Emend, Aloxi+Emend+corticosteroid, 5-HT_3RA+Emend, Emend+corticosteroid were prescribed during the acute phase for prevention of CINV.

Past CINV Experience of Study Participants

The past experiences of CINV of study respondents are reported in Table 4-35. Compared to 44.2% of patients experiencing nausea, only 23.3% of respondents experienced emesis following chemotherapy. Among patients experiencing nausea, the mean severity as reported using a 100mm VAS was found to be 50.3 (SD=25.1). Of the respondents who experienced emesis, almost 82.1% of them reported experiencing 1-2 emetic episodes following chemotherapy.

Table 4-34: Clinical Characteristics of Respondents

Clinical Characteristics	N (%) Total N = 120
Type of Cancer	
Breast	34 (28.3%)
Lung	28 (23.3%)
Colorectal	16 (13.3%)
Urogenital	19 (15.8%)
Respiratory	2 (1.7%)
Other	19 (15.8%)
Unknown	2 (1.7%)
Cycle of Chemotherapy	
Chemotherapy-naïve	22 (18.3%)
Received in last 3 months	6 (5.0%)
1st cycle of new regimen	11 (9.2%)
> 1 cycle of chemotherapy	81 (67.5%)
Type of Chemotherapy Regimen	
HE (Cisplatin-based)	13 (10.8%)
HE (Non-cisplatin)	55 (45.8%)
ME (30-90%)	27 (22.5%)
LE (10-30%)	23 (19.2%)
Unable to classify	2 (1.7%)
Antiemetic Regimen – Acute Phase	
5-HT_3RA + Corticosteroid	65 (54.2%)
Emend + 5-HT_3RA + Corticosteroid	10 (8.3%)
Aloxi + Corticosteroid	20 (16.7%)
Only 5-HT_3RA	13 (10.8%)
Other single agent regimen[a]	5 (4.2%)
Other combination regimens[b]	6 (5%)

[a] Includes either corticosteroid or Aloxi or Emend or compazine
[b] Includes either Aloxi+Emend, Aloxi+Emend+corticosteroid, 5-HT_3RA+Emend, Emend+Corticosteroid

Table 4-35: Past Experience of Chemotherapy-Induced Nausea and Vomiting (CINV)

Past Experience of CINV	N (%)
Experience of nausea during last cycle	
Yes	53 (44.2%)
No	37 (30.8%)
Not Applicable	30 (25.0%)
Severity of Nausea (N = 53), Mean (SD)	50.3 (25.1)
Experience of emesis during last cycle	
No	62 (51.7%)
1-2 episodes	23 (19.2%)
3-5 episodes	4 (3.3%)
> 5 episodes	1 (0.8%)
Not applicable	30 (25.0%)

Results for Objectives 2.1 and 2.2

Scenario 1 – Emetic Control Following Administration of Highly Emetogenic Chemotherapy

Scenario 1 of the survey described the improvement in the probability of acute and delayed emesis control due to the addition of new drug (aprepitant) to the standard regimen of 5-HT_3RA and dexamethasone for prevention of CINV due to highly emetogenic chemotherapy. The results in Table 4-36 show the level of importance that respondents place on improved emesis control in the acute and delayed phase. The mean perceived level of importance for reduction in the probability of acute emesis from 30% to 17% due to the addition of new drug was 8.8 (SD=1.7) and reduction in the probability of delayed emesis from 55% to 37% was 9.2 (SD=1.5). Due to ordinal nature of the dependent variable, Wilcoxon signed rank test was used to test for significant differences in the perceived level of importance of improvements in acute emesis and delayed emesis. The null hypothesis tested was that there are no significant differences in the perceived importance of the acute emesis control and delayed emesis control. It is evident from the results shown in Table 4-36 that the respondents perceived delayed emesis control to be of greater importance as compared to the acute emesis control.

The WTP results for scenario 1 are shown in Table 4-37. Though all respondents preferred the addition of the new drug to the standard regimen compared to receiving only the standard regimen, approximately 91% (N =109) gave positive WTP value for receiving the new drug for a 3-day regimen. Out of 11 respondents who reported that they would not pay anything out-of-pocket to receive the new drug, two gave zero values reflective of "protest zeroes". The remaining nine respondents genuinely placed zeroes as they were unable to afford out-of-pocket payments for the new drug. Thus, among 109 respondents who gave a positive WTP value for the 3-day regimen of the new drug, the mean WTP was $89.90 (SD=101.90) and median was $60.00.

Due to the non-normal distribution of the WTP amounts, Mann-Whitney U test was used to test whether the maximum WTP differed based on the order of scenarios presented. The results in Table 4-38 indicate that the WTP amounts for scenario 1 did not differ significantly based on the order of scenarios presented. The results are presented for the sample without protest zeroes and for the sample with only positive WTP values.

Respondents were also asked to state the reasons for preferring the addition of the new drug to the standard regimen. About 60.0% of the respondents provided a reason for preferring

the new regimen for prevention of CINV due to highly emetogenic chemotherapy. A majority of respondents (N = 18) reported that they would take anything that would prevent them from getting “sick”, and nausea and vomiting were unpleasant and painful. Sixteen respondents reported that they prefer the new drug as it will increase their ability to eat more, maintain their weight, sleep well, go to work and get on with their daily activities. One sixth of the respondents preferred the new drug in addition to the standard regimen due to its ability to better control nausea and vomiting. The impact of nausea and vomiting on quality of life was mentioned as one of reasons for preference of the new drug by eight respondents.

Table 4-36: Perceived level of importance of improved emesis control (Scenario 1)

Item (N = 120)	Mean (SD)	Median	Z value	Significance
			- 4.712	0.000*
Perceived level of importance – Acute emesis	8.8 (±1.72)	10.0		
Perceived level of importance – Delayed emesis	9.2 (±1.51)	10.0		

Table 4-37: Willingness-to-Pay Results for Scenario 1

WTP Values	N (%)	
Non-zero values	109 (90.8%)	
Protest zeroes	2 (1.7%)	
Genuine zeroes	9 (7.5%)	
	Mean (SD)	**Median**
Maximum WTP amount for 3 days of aprepitant for overall control of emesis (N = 118)	$83.1 (100.8)	$50.0
Maximum WTP amount for 3 days of aprepitant for overall control of emesis (N = 109)	$89.9 (101.9)	$60.0

Table 4-38: Differences in Willingness-to-Pay Based on the Order of Scenarios Presented – For Scenario 1.

Item	Mean (SD)	Median (Range)	Z value	P value
For sample without protest zeroes (N = 118)			-0.008	0.994
Maximum WTP amount for 3 days of aprepitant – Version A (N = 59)	87.1 (±117.22)	45.00 (0.00-600.00)		
Maximum WTP amount for 3 days of aprepitant – Version B (N = 59)	79.1 (±81.96)	60.00 (0.00 – 300.00)		
For sample without all zeroes (N = 109)				
Maximum WTP amount for 3 days of aprepitant – Version A (N = 55)	93.4 (±118.97)	50.00 (3.00-600.00)	-0.189	0.850
Maximum WTP amount for 3 days of aprepitant – Version B (N = 54)	86.4 (±81.89)	60.00 (5.00 – 300.00)		

Scenario 2 – Emetic Control Following Administration of Moderately Emetogenic Chemotherapy

The scenario 2 described the improved emesis control due to single injection of palonosetron instead of the standard regimen of 5-HT_3RA and dexamethasone for prevention of CINV following administration of moderately emetogenic chemotherapy. The acute control of emesis was assumed to be equivalent between the two regimens. The mean perceived level of importance of reducing the chance of delayed emesis from 45% to 33% was 8.6 (SD=1.6). Out of 120 respondents, only one did not prefer the new drug and the reasons reported were "dislike of injection" and "12% risk reduction of emesis is not much".

The WTP results for scenario 2 are shown in Table 4-39. Of those respondents who preferred the new drug, approximately 91% (N =109) gave positive WTP value for receiving the new drug for a 3-day regimen. Out of 11 respondents who reported that they would not pay anything out-of-pocket to receive the new drug, two gave zero values reflective as "protest zeroes". The remaining nine respondents genuinely placed zeroes as they were unable to afford out-of-pocket payments for the new drug. Thus, among 108 respondents who gave a positive WTP value for the single injection of the new drug, the mean WTP was $83.5 (SD=94.5) and median was $55.0. The results of the Mann-Whitney U test reported in Table 4-40 indicate that the WTP amounts for scenario 2 did not differ significantly based on the order of scenarios presented. The results are presented for the sample without protest zeroes and for the sample with only positive WTP values.

Respondents were also asked to state the reasons for preferring the new drug to the standard regimen in scenario 2. About 61.0% of the respondents provided a reason for preferring the new regimen for prevention of CINV due to moderately emetogenic chemotherapy. Approximately one fourth of respondents (N = 18) reported that they prefer the new drug as it is to be taken as a one-time injection instead of a multi-day regimen. The other reasons for preferring the new drug included better control of emesis, ability of get back to work, do daily activities, ability to eat and maintain weight. The impact of nausea and vomiting on quality of life was mentioned as one of reasons for preference of the new drug by three respondents.

Wilcoxon signed rank test was used to test if there were significant differences in the maximum WTP based on the scenario. As shown in Table 4-41, scenario 1 the median WTP for scenario 1 was significantly higher than that for scenario 2 for the sample without protest zeroes

and sample without any zeroes. The level of difficulty in understanding the hypothetical scenarios and in answering the WTP questions was assessed using a 11-point Likert type scale. The mean level of difficulty in understanding the scenarios was 1.5 (SD=1.74) and in answering the WTP questions was 2.5 (SD=2.5). About 4% of the study population reported a score of greater than 5 for the level of difficulty in understanding the hypothetical scenarios. On the other hand, about 15% of respondents reported a score of greater than 5 for the level of difficulty in answering the WTP question.

Table 4-39: WTP Results for Scenario 2

WTP Values*	N (%)	
Non-zero values	108 (90.8%)	
Protest zeroes	2 (1.7%)	
Genuine zeroes	9 (7.6%)	
	Mean (SD)	**Median**
Maximum WTP amount for a single injection of palonosetron for overall control of emesis (N = 117)	$77.1 (93.45)	$45.0
Maximum WTP amount for a single injection of palonosetron for overall control of emesis (N = 108)	$83.5 (94.5)	$55.0

* Sample includes those who preferred new drug compared to the standard regimen (N = 119)

Table 4-40: Differences in WTP results based on the order of scenarios presented – For Scenario 2.

Item	Mean (SD)	Median (Range)	Z value	P value
For sample without protest zeroes (N = 117)			-0.359	0.720
Maximum WTP amount for single injection of palonosetron – Version A (N = 59)	80.1 (±106.04)	45.00 (0.00-600.00)		
Maximum WTP amount for single injection of palonosetron – Version B (N = 58)	74.0 (±79.45)	47.5 (0.00-300.00)		
For sample without all zeroes (N = 108)			-0.210	0.834
Maximum WTP amount for single injection of palonosetron – Version A (N = 55)	85.9 (±107.55)	50.00 (3.00 – 600.00)		
Maximum WTP amount for single injection of palonosetron – Version B (N = 53)	81.0 (±79.64)	60.00 (5.00 – 300.00)		

Table 4-41: Differences in maximum WTP amounts between scenarios

Item	Mean (SD)	Median (range)	Z value	P value
Sample without protest zeroes			-2.879	0.004*
Maximum WTP for scenario 1	83.4 (±101.15)	50.00 (0.00 – 600.00)		
Maximum WTP for scenario 2	77.1 (±93.45)	45.00 (0.00 – 600.00)		
Sample without zeroes			-2.879	0.004*
Maximum WTP for scenario 1	90.4 (±102.27)	60.00 (3.00 – 600.00)		
Maximum WTP for scenario 2	83.5 (±94.48)	55.00 (3.00 – 600.00)		

Results for Objectives 2.3 and 2.4

Differences in WTP for scenario 1 based on demographic and clinical characteristics

The differences in maximum WTP amount for scenario 1 based on demographic and clinical characteristics are presented in Table 4-42. Due to the non-normal nature of the WTP data, non parametric statistics were employed. Mann Whitney U test was used to test for differences in WTP for factors with two groups while Kruskal-Wallis test was used for factors with more than two groups. To determine which groups are significantly different from each other following a significant Kruskal-Wallis test result, post hoc tests using Mann Whitney U test were conducted. The results displayed are for the sample with only positive WTP values.

WTP for scenario 1 differed significantly based on education level completed, employment status and annual household income level. There were no significant differences in WTP for scenario 1 based on age, gender, number of members in the household and marital status. Post hoc tests showed that respondents who completed HS (Z value = -2.357, p value = 0.018) and respondents with higher than HS education (Z value = -3.514, p value = 0.000) reported significantly higher WTP as compared to respondents who did not complete HS. There was no significant difference in the WTP between respondents with high school education and those with greater than high school education (Z value = -1.717, p value = 0.086). Post hoc tests showed that respondents who reported annual household income in the range $30,000-$60,000 (Z value = -5.207, p value = 0.000) and respondents with higher than ≥ 60,000 (Z value = -5.464, p value = 0.000) reported significantly higher WTP as compared to respondents who with annual household income ≤ $30,000. There was no significant difference in the WTP amount between respondents with annual household income level in the range $30,000-$60,000 and those with ≥ 60,000 (Z value = -0.512, p value = 0.609). Mann-Whitney U test showed that employed respondents reported significantly higher WTP as compared to those who were unemployed or retired. Results in Table 4-43 shows that there are no significant differences in WTP for scenario 1 based on clinical characteristics such as previous chemotherapy experience, previous experience of CINV, and level of emetogenicity of the chemotherapy regimen.

Differences in WTP for scenario 2 based on demographic and clinical characteristics

Results of Bivariate Analyses

The differences in maximum WTP amount for scenario 2 based on demographic and clinical characteristics are presented in Table 4-44. WTP for scenario 2 differed significantly based on highest level of education completed and annual household income level. There were no significant differences in WTP for scenario 2 based on age, gender, number of members in the household, employment status and marital status.

Post hoc tests showed that respondents who completed HS (Z value = -1.990, p value = 0.047) and respondents with more than HS education (Z value = -3.053, p value = 0.002) reported significantly higher WTP as compared to respondents who did not complete HS. There was no significant difference in the WTP between respondents with high school education and those with greater than high school education (Z value = -1.193, p value = 0.233). Post hoc tests showed that respondents who reported annual household income in the range $30,000-$60,000 (Z value = -5.111, p value = 0.000) and respondents with higher than ≥ 60,000 (Z value = -4.909, p value = 0.000) reported significantly higher WTP as compared to respondents who with annual household income ≤ $30,000. There was no significant difference in the WTP amount between respondents with annual household income level in the range $30,000-$60,000 and those with ≥ 60,000 (Z value = -0.315, p value = 0.752).

Results in Table 4-45 shows that there are no significant differences in WTP for scenario 2 based on clinical characteristics such as previous chemotherapy experience, previous experience of CINV, and level of emetogenicity of the chemotherapy regimen.

Table 4-42: Differences in maximum WTP amount based on demographic characteristics – Scenario 1

Demographic Characteristics	Mean WTP	Median (range)	Z value	p value
Age			0.439	0.803
<45 years	78.2 (53.47)	75.00 (10.00-200.00)		
45-64 years	86.6 (101.71)	50.00 (3.00-500.00)		
≥65 years	102.4 (122.72)	60.00 (10.00-600.00)		
Gender			-0.813	0.416
Male	105.8 (124.52)	60.00 (5.00-600.00)		
Female	80.0 (84.22)	60.00 (3.00-500.00)		
Education Level[a]			12.678	0.002*
Less than high school education	35.3 (24.75)	30.00 (10.00-100.00)		
Completed high school education	77.8 (72.10)	60.00 (3.00-300.00)		
More than high school education	121.3 (132.00)	75.00 (10.00-600.00)		
Marital Status			-0.686	0.492
Married	95.8 (110.5)	60.00 (3.00-600.00)		
Not Married/Single/Divorced/Widowed	67.8 (55.8)	45.00 (5.00-200.00)		
Employment			-2.484	0.013*
Not working	77.3 (90.97)	45.00 (3.00-600.00)		
Working (Part-time or Full-time)	122.7 (121.74)	75.00 (5.00-500.00)		
Annual Household Income Level[a]			40.595	0.000*
≤$30,000	37.5 (32.79)	30.00 (3.00-150.00)		
$30,001 - $60,000	114.0 (85.50)	100.00 (15.00-300.00)		
>$60,000	141.3 (145.03)	100.00 (10.00-600.00)		

Table 4-42 (Continued): Differences in maximum WTP amount based on demographic characteristics – Scenario 1

Demographic Characteristics	Mean WTP	Median (range)	Z value	p value
Number of Members in the Household			5.746	0.057
Zero	63.3 (52.84)	35.00 (20.00-200.00)		
One member	78.1 (93.16)	47.50 (5.00-600.00)		
More than one member	120.1 (122.71)	100.00 (3.00-500.00)		

Table 4-43: Differences in maximum WTP amount based on clinical characteristics – Scenario 1

Clinical Characteristics	Mean (SD)	Median (range)	Z value	p value
Presence of nausea and vomiting			5.060	0.080
Neither nausea nor vomiting	86.9 (105.08)	45.00 (3.00-500.00)		
Either nausea or emesis or both	109.2 (118.30)	75.00 (5.00-600.00)		
Not applicable	58.5 (42.00)	50.00 (10.00-150.00)		
Past chemotherapy experience			-0.971	0.331
Chemotherapy naïve	59.5 (39.57)	50.00 (10.00-150.00)		
Current or past experience	96.8 (110.20)	60.00 (3.00-600.00)		
Level of emetogenicity			1.269	0.530
Highly emetogenic	85.9 (104.90)	50.00 (5.00-600.00)		
Moderately emetogenic	102.0 (92.52)	75.00 (3.00-300.00)		
Low or not emetogenic	79.2 (98.60)	60.00 (5.00-500.00)		

Table 4-44: Differences in maximum WTP amount based on demographic characteristics – Scenario 2

Demographic Characteristics	Mean (SD)	Median (range)	Z value	p value
Age			0.503[a]	0.777
<45 years	75.8 (53.94)	75.00 (5.00-200.00)		
45-64 years	79.4 (88.46)	37.50 (3.00-500.00)		
≥65 years	94.9 (120.67)	50.00 (8.00-600.00)		
Gender			-0.754[b]	0.451
Male	94.2 (110.71)	60.00 (5.00-600.00)		
Female	76.7 (82.71)	47.50 (3.00-500.00)		
Education Level			8.709	0.013*
Less than high school education	35.7 (23.67)	30.00 (5.00-100.00)		
Completed high school education	78.3 (75.06)	60.00 (3.00-300.00)		
More than high school education	105.6 (120.04)	75.00 (8.00-600.00)		
Marital Status			-0.770	0.442
Married	90.0 (103.14)	60.00 (3.00-600.00)		
Not Married/Single/Divorced/Widowed	59.6 (45.07)	35.00 (5.00-200.00)		
Employment			-1.857	0.063
Not working	75.9 (91.50)	40.00 (3.00-600.00)		
Working (Part-time or Full-time)	102.3 (100.58)	75.00 (5.00-500.00)		
Annual Household Income Level[a]			35.884	0.000*
≤$30,000	36.6 (32.68)	30.00 (3.00-150.00)		
$30,001 - $60,000	106.5 (80.00)	100.00 (15.00-300.00)		
>$60,000	129.5 (136.11)	100.00 (10.00-600.00)		

Table 4-44 (Continued): Differences in maximum WTP amount based on demographic characteristics – Scenario 2

Demographic Characteristics	Mean (SD)	Median (range)	Z value	p value
Number of Members in the Household			4.684	0.096
Zero	53.8 (34.45)	35.00 (20.00-100.00)		
One member	79.2 (93.85)	45.00 (5.00-600.00)		
More than one member	106.5 (105.88)	75.00 (3.00-500.00)		

Table 4-45: Differences in maximum WTP amount based on demographic characteristics – Scenario 2

Clinical Characteristics	Mean (SD)	Median (range)	Z value	p value
Presence of nausea and vomiting			5.532	0.063
Neither nausea nor vomiting	77.1 (85.76)	35.00 (3.00-300.00)		
Either nausea or emesis or both	103.3 (116.34)	75.00 (5.00-600.00)		
Not applicable	56.5 (41.75)	42.50 (8.00-150.00)		
Past chemotherapy experience			-0.974	0.330
Chemotherapy naïve	56.9 (39.28)	42.50 (8.00-150.00)		
Current or past experience	89.6 (102.18)	60.00 (3.00-600.00)		
Level of emetogenicity			1.405	0.495
Highly emetogenic	79.1 (91.67)	50.00 (5.00-600.00)		
Moderately emetogenic	93.8 (86.89)	75.00 (3.00-300.00)		
Low or not emetogenic	75.6 (102.41)	40.00 (5.00-500.00)		

Results of Multivariate Analyses

Multivariate analyses conducted to determine the association between WTP and demographic and clinical characteristics. The relevant covariates for inclusion in the regression models were identified based on the results of the bivariate analyses which were presented in the previous section. This is a recommended approach for removing unimportant covariates so that a more manageable set of variables can be submitted to multivariate techniques (George, 1988). The preset α value for screening variables for inclusion in the model was set at 0.15. Based on the criteria, the variables included in the regression models were age, employment status, level of education completed, annual household income, number of members in the household and past experience with CINV. Correlation analysis was conducted to test for multicollinearity among the independent variables. Although significant positive correlations of 1) annual household income with education, 2) income with employment, and 3) education with employment were found the magnitude of correlation was low. Thus, all three variables were included in the regression models.

Results for Scenario 1

Table 4-46 shows results of ordinary least squares (OLS) and semi-logarithmic regression models employed to determine the association between WTP and various respondent characteristics for scenario 1. The use of semi-logarithmic regression model did not lead to any changes in the significance of the variables but lead to changes in the sign of the regression coefficients, when compared to OLS results. The results of the OLS model showed no significant association of WTP with employment status, highest level of education completed, number of members in the household and past experience of CINV. There was a significant association between WTP and annual household income level. Respondents with annual household income level between $30,001 and $60,000 were willing to pay $62.85 more and those with >$60,000 were willing to pay $76.35 more compared to those with income ≤$30,000.

Results of the semi-log model showed significant differences in WTP amount based on the annual household income level. Respondents with annual household income level between $30,001 and $60,000 were willing to pay approximately 179% more as compared to those respondents with income ≤$30,000. Similarly, respondents with annual household income >$60,000 were willing to pay approximately 198% more compared to those respondents with

income ≤$30,000. Although not significant, patients who had received chemotherapy but did not experience nausea or vomiting reported lower WTP amounts compared to those who never had chemotherapy. On the other hand, patients who had experienced nausea/vomiting or both in the past reported higher WTP amounts as compared to those who never had chemotherapy.

Results for Scenario 2

Table 4-47 shows results of ordinary least squares (OLS) and semi-logarithmic regression models employed to determine the association between WTP and various respondent characteristics for scenario 2. The use of semi-logarithmic regression model did not lead to any changes in the significance of the variables but lead to changes in the sign of the regression coefficients, when compared to OLS results. The results of the OLS model showed no significant association of WTP with employment status, highest level of education completed, number of members in the household and past experience of CINV. There was a significant association between WTP and annual household income level. Respondents with annual household income level between $30,001 and $60,000 were willing to pay $62.50 more and those with >$60,000 were willing to pay $81.27 more compared to those with income ≤$30,000.

Results of the semi-log model showed significant differences in WTP amount based on the annual household income level. Respondents with annual household income level between $30,001 and $60,000 were willing to pay approximately 182% more as compared to those respondents with income ≤$30,000. Similarly, respondents with annual household income >$60,000 were willing to pay approximately 209% more compared to those respondents with income ≤$30,000.

Table 4-46: Multivariate analysis to test the association between WTP and annual household income – Scenario 1

Demographic Characteristics	Linear Regression		Semi-logarithmic	
	β coefficient	*P value*	*β coefficient*	*P value*
Age	2.078	0.043*	0.008	0.407
Employed	30.145	0.225	0.144	0.527
Highest Level of Education Completed				
Completed High School	30.714	0.269	0.388	0.129
More than High School	43.980	0.148	0.437	0.117
Annual Household Income				
$30,001 - $60,000	62.845	0.005*	1.045	0.000*
>$60,000	76.349	0.004*	1.122	0.000*
Number of Members in the Household	14.408	0.145	-0.004	0.962
Past Experience of CINV				
Neither nausea nor emesis	15.121	0.537	-0.071	0.750
Either Nausea and/or emesis	22.805	0.344	0.203	0.358
F-statistic	3.894		6.854	
Adjusted R^2	19.4%		32.8%	

Table 4-47: Multivariate analysis to test the association between WTP and annual household income – Scenario 2

Demographic Characteristics	Linear Regression		Semi-logarithmic	
	β coefficient	*P value*	*β coefficient*	*P value*
Age	1.516	0.117	0.004	0.670
Employed	6.664	0.777	0.013	0.954
Highest Level of Education Completed				
Completed High School	34.826	0.186	0.396	0.126
More than High School	35.434	0.218	0.360	0.202
Annual Household Income				
$30,001 - $60,000	62.499	0.003	1.058	0.000
>$60,000	81.271	0.001	1.158	0.000
Number of Members in the Household	9.085	0.331	-0.056	0.544
Past Experience of CINV				
Neither nausea nor emesis	8.502	0.713	-0.111	0.627
Either Nausea and/or emesis	21.578	0.345	0.226	0.314
F-statistic	3.297		6.173	
Adjusted R^2	16.2%		30.3%	

Results for Objective 2.5

Net Benefit of Adding Aprepitant to the Standard Regimen

The standard regimen and the new regimen for prevention of CINV considered in scenario 1 are shown in Table 4-48. The costs of the regimens per patient per cycle were calculated using the drug prices presented in Table 3-7. The base case results for the cost benefit analysis for prevention of CINV following HE chemotherapy are presented in Table 4-48. The incremental benefit of adding aprepitant to the standard regimen of a 5-HT_3RA and corticosteroid for prevention of CINV due to HE chemotherapy was $89.90 (SD=$101.9, 95% CI = $70.77-$109.03). The total cost of the new regimen and the standard regimen was $529.29 and $233.10, respectively resulting in the incremental cost for the new regimen to be $296.11. Since the incremental costs were greater than the benefits, the net cost of the new regimen was calculated by subtracting the incremental benefits from the incremental costs. The net costs for the new regimen in patients receiving HE chemotherapy was $206.21 (95% CI = $187.08 - $225.34).

Sensitivity Analysis

Sensitivity analysis was conducted to test the robustness of the results by varying the total cost of the new and the standard regimens. The variations in costs were based on variations in dosage and route of administration of the antiemetic drugs in the two regimens. Table 4-49 shows the results of four scenarios to study impact of variations in the prophylactic antiemetic regimens on the net benefit of the new antiemetic regimens.

Scenario A involved replacing IV ondansetron 32mg with oral ondansetron 8mg as prior evidence suggest equivalent efficacy of the two doses. The incremental costs of the new regimen were still higher compared to the incremental benefits and the net costs ranged from $356.77-$395.03. The incremental benefits were higher compared to the incremental costs in Scenario B where the combination of a 5-HT_3RA and corticosteroid were used in the delayed phase. The analyses conducted with the 95% CI of WTP estimates revealed that the net benefits ranged between -$30.09 and $8.17 and this suggests a situation of cost neutrality. For scenario C, the net costs were insensitive to the changes in the dose of ondansetron and the delayed phase regimen. Scenario D involved varying the dose of ondansetron in the new regimen and this resulted in the decrease in the net costs associated with the new regimen. Overall, the results suggest that the net costs associated with the new regimen is highly sensitive to the total costs of

the new and standard regimen based on the drug dose and route of administration employed in the study.

Table 4-48: Incremental costs, Incremental Benefits and Net Benefit of New Antiemetic Regimen for HE Chemotherapy

Regimen	Total Costs*	Incremental Costs (IC)	Incremental Benefits (IB)	Net Benefit (IC – IB)
NEW REGIMEN				
Acute phase - Aprepitant 125 mg + IV Ondansetron 32 mg + Oral Dexamethasone 12 mg Delayed phase – Aprepitant 80 mg (Days 2-3) Oral Dexamethasone 8mg (Days 2-4)	$529.29			
STANDARD REGIMEN – Baseline				
Acute phase - IV Ondansetron 32 mg + Oral Dexamethasone 20 mg Delayed phase – Oral Dexamethasone 8 mg BID (Days 2-4)	$233.18	$296.11	$89.90 ($70.77-$109.03)	$206.21 ($187.08-$225.34)

* Total cost of the regimen includes the cost of the prophylactic antiemetic drugs and the administration cost of the IV drugs

Table 4-49: Sensitivity Analysis Results Based on Changes in the Drug Dosage and Route of Administration

Regimen	Total Costs	Incremental Costs (IC)	Incremental Benefits (IB)	Net Benefit (IC – IB)
NEW REGIMEN				
Acute phase - Aprepitant 125 mg + IV Ondansetron 32 mg + Oral Dexamethasone 12 mg Delayed phase – Aprepitant 80 mg (Days 2-3) Oral Dexamethasone 8mg (Days 2-4)	$529.29			
STANDARD REGIMEN – Scenario A				
Acute phase - Oral Ondansetron 8 mg + Oral Dexamethasone 20 mg Delayed phase – Oral Dexamethasone 8 mg BID (Days 2-4)	$63.49	$465.80*	$89.90 ($70.77-$109.03)	$375.90 ($356.77-$395.03)
STANDARD REGIMEN – Scenario B				
Acute phase - IV Ondansetron 32 mg + Oral Dexamethasone 12 mg Delayed phase – Oral Dexamethasone 8 mg BID (Days 2-3) and 8mg on Day 4 + Oral Ondansetron 8mg BID (Days 2-4)	$450.35	$78.94*	$89.90 ($70.77-$109.03)	-10.96 (-$30.09 -$8.17)
STANDARD REGIMEN – Scenario C				
Acute phase - Oral Ondansetron 8 mg + Oral Dexamethasone 20 mg Delayed phase – Oral Dexamethasone 8 mg BID (Days 2-3) and 8mg on Day 4 + Oral Ondansetron 8mg BID (Days 2-4)	$280.66	$248.63*	$89.90 ($70.77-$109.03)	$158.73 ($138.70-$177.86)
NEW REGIMEN – Scenario D				
Acute phase - Aprepitant 125 mg + Oral Ondansetron 8 mg + Oral Dexamethasone 12 mg Delayed phase – Aprepitant 80 mg (Days 2-3) Oral Dexamethasone 8mg (Days 2-4)	$359.90	$126.72**	$89.90 ($70.77-$109.03)	$36.82 ($19.13-$55.95)

* Calculated by subtracting total cost of the regimen from the total cost of the new regimen

** Calculated by subtracting the total cost of standard regimen – baseline ($233.18) from the cost of the new regimen –Scenario D.

Results for Objective 2.6

Net Benefit of Using Palonosetron instead of the Standard Regimen

Scenario 2 of the WTP survey involved substituting palonosetron for preventing CINV following ME chemotherapy instead of the standard regimen of a 5-HT_3RA and corticosteroid. The incremental costs, incremental benefits and net costs associated with the use of palonosetron are reported in Table 4-50. The net cost of palonosetron for prevention of CINV following ME chemotherapy for one cycle is $160.99. The net costs due to the new regimen of palonosetron were recalculated using the 95% CI of the maximum WTP which resulted in the net costs within the range $143.17-$178.81. Thus, the results were insensitive to the extremes in the WTP.

Sensitivity Analysis

Sensitivity analysis was conducted to test the robustness of the results by varying the total cost of the new and the standard regimens. The sensitivity analyses were conducted by varying the total cost of the regimens. The costs varied based on the changes in the delayed phase regimen employed for prevention of CINV following ME chemotherapy. Table 4-51 shows the results of two scenarios designed to study the impact of variations in the prophylactic antiemetic regimens on the net benefit of the new antiemetic regimens. Scenario A involved calculating the net costs of the palonosetron regimen compared to a single IV dose of ondansetron 32 mg. The net costs decreased as compared to the base case results but were still indicative that the incremental costs of the palonosetron regimen exceeded the incremental benefits. Scenario B involved calculating the net costs associated with employing a combination regimen of a 5-HT_3RA and dexamethasone in the delayed phase of the standard regimen. Due to the high total costs of the standard regimen under scenario B, as compared to the new regimen, the former regimen was dominated by the new regimen.

Table 4-50: Incremental costs, Incremental Benefits and Net Benefit of New Antiemetic Regimen for ME Chemotherapy

Regimen	Total Costs*	Incremental Costs (IC)	Incremental Benefits (IB)	Net Benefit (IC – IB)
NEW REGIMEN				
Acute phase - IV Palonosetron 0.25mg	$340.20			
STANDARD REGIMEN				
Acute phase – IV Ondansetron 8mg + IV Dexamethasone 8 mg Delayed Phase – Oral Dexamethasone 4mg BID (Days 2-5)	$95.71	$244.49	$83.50 ($65.68-$101.32)	$160.99 ($143.17-$178.81)

* Total cost of the regimen includes the cost of the prophylactic antiemetic drugs and the administration cost of the IV drugs

Table 4-51: Sensitivity Analysis Results Based on Changes in the Drug Dosage and Route of Administration for HE Chemotherapy

Regimen	Total Costs	Incremental Costs (IC)	Incremental Benefits (IB)	Net Benefit (IC – IB)
NEW REGIMEN				
Acute phase – IV Palonosetron 0.25mg	$340.20			
Standard Regimen – Scenario A				
Acute phase – IV Ondansetron 32mg	$206.41	$133.79	$83.50 ($65.68-$101.32)	$50.29 ($32.47-$68.11)
Standard Regimen – Scenario B				
Acute phase - IV Ondansetron 8mg + IV Dexamethasone 8 mg Delayed phase – Oral Dexamethasone 4 mg BID (Days 2-5) + Oral Ondansetron 4mg BID (Days 2-5)	$389.47	-$49.27	$83.50 ($65.68-$101.32)	Dominated*

* Regimen in Scenario B is dominated by the new regimen as the latter costs less and provides increased emesis protection

CHAPTER FIVE

DISCUSSION AND RECOMMENDATIONS

The primary goal of this study was to conduct a comprehensive economic evaluation of prophylactic antiemetic regimens for prevention of chemotherapy-induced nausea and vomiting (CINV) following administration of highly emetogenic (HE) and moderately emetogenic (ME) chemotherapy. The introduction of more efficacious but more costly new antiemetic agents for prevention of CINV may pose a significant economic burden on payers, hospital formularies and society. In Phase I of the study, two decision models were developed to quantify the costs and benefits of the various antiemetic regimens for prevention of CINV due to HE and ME chemotherapy. A contingent valuation survey was developed in Phase II to estimate the monetary value of improved emesis control due to the new antiemetic regimens among cancer patients. The detailed methodology for determination of cost-effectiveness of the alternative antiemetic regimens and estimating the maximum willingness-to-pay (WTP) for improved emesis control is reported in Chapter 3. The results of the decision models and the survey are presented in Chapter 4. This chapter discusses the major study findings and their implications. It also includes the major limitations of the study and presents the significance of the study results. Finally some recommendations for future research are also included in this chapter.

5.1: Review of Phase I Findings

The introduction of more efficacious but more costly new antiemetic agents for prevention of CINV may pose a significant economic burden on payers, hospital formularies and society. Cost-effectiveness analysis is an economic evaluation method used to compare new treatments to standard of care to make informed decision-making. The incremental cost-effectiveness (ICER) was calculated as the additional cost of the new treatment divided by the increased benefit of the new treatment. Two decision models were developed to determine the costs, effectiveness and incremental cost-effectiveness ratios of prophylactic antiemetic regimens for prevention of CINV due to HE and ME chemotherapy. The cost-effectiveness analyses were conducted from both the payer and societal perspective.

For Highly Emetogenic Chemotherapy Model

Results from the payer and societal perspectives showed that the cost for complete control of emesis in one patient is the lowest for regimen C and the highest for regimen A. When comparing only the resource utilization and not the effectiveness of the treatment strategies, regimen A was approximately three times more expensive than regimen C from the payer perspective. The lower acquisition cost of regimen C was the principal driving force that resulted in a lower overall cost of the primary therapy. The ratio decreased to 2.5 times when the effectiveness of the regimens were used in the calculations. However, the differential in the total cost of the aprepitant regimen was not compensated for fully by the superior efficacy and lower resource utilization during the delayed phase. From the payer perspective, the base-case analysis yielded an incremental cost-effectiveness ratio (ICER) of $3,363.181 per patient with complete control of emesis for regimen A (addition of aprepitant to the standard regimen of a 5-HT_3RA and dexamethasone) compared to regimen C (included metoclopramide in the delayed phase). Regimens B and D were dominated by regimen C and were excluded from the ICER calculations. The ICER for regimen A was found to be $2,881.605 per patient with complete control of emesis from the societal perspective.

One-way sensitivity analysis was conducted to identify key variables that may have an impact on the ICERs of the treatment regimens. The ICER of the regimens were sensitive to the probability of no acute emesis, the probability of no delayed emesis given no acute emesis, and the probability of receiving rescue medications in the delayed phase given no delayed emesis. Increasing the probability of no delayed emesis given no acute emesis for regimen D resulted in changes in the dominance status of the regimens. Regimen D was no longer dominated by regimen C and had an ICER of $2,173 per patient with complete control of emesis from the payer perspective and $1,787 from the societal perspective. The results were not very sensitive to changes in the total cost of prophylactic antiemetic regimens, infusion costs, costs of IV ondansetron and cost of aprepitant. The total costs and ICER for each regimen were not sensitive to variations in the number of hours of lost productivity and the average wages per hour.

The cost effectiveness results were sensitive to the model including the side effects associated with regimen C (includes metoclopramide in the delayed phase). The ICER for regimen A decreased from both payer and societal perspectives and regimen D was excluded from the calculations due to extended dominance. Across all the sensitivity analyses, regimen C

remained the least expensive treatment, though the cost-effectiveness of the regimen varied with changes in the parameter estimates.

Although simple sensitivity analysis can be helpful in identifying factors that affect CE ratios, single value analysis can be extremely misleading. In reality, within the possible ranges of each variable, thousands of possible combinations of values can exist. In this study, probabilistic sensitivity analysis (second-order Monte Carlo simulation method) was conducted to take into account all parameter variations simultaneously. Results from the probabilistic sensitivity analyses for the HE model showed that the expected mean costs and effectiveness were similar to those obtained in the base case analysis. There were no changes in dominance status of the regimens, though the ICERs for regimen A were higher as compared to the base case analysis, from the payer and societal perspectives.

This study is among the first to evaluate the cost-effectiveness of four antiemetic regimens, new regimen A (addition of aprepitant to the standard regimen), regimen B (standard used in aprepitant clinical trials), regimen C (recommended by ASCO 1999 guidelines) and regimen D (most common clinical practice) for prevention of CINV following HE chemotherapy. Currently, three studies evaluating the cost-effectiveness of adding aprepitant to the standard regimen have been published in abstract format (Deuson, 2004; Ehlken et al., 2004; Moore et al., 2005). These studies have evaluated the cost effectiveness of addition of aprepitant to the standard regimen but have not compared it to regimens used commonly in clinical practice. The results of the study may not be directly comparable to the three published economic evaluations due to the differences in the treatment comparators, perspective, time horizons and methodology employed.

Ehlken and colleagues (2004) conducted a study in office-based settings in Germany to determine the incremental costs and effects associated with addition of aprepitant to the standard regimen from the payer perspective. The ICER for aprepitant regimen was calculated to be €21,764 per quality-adjusted life years (QALY). The published abstract does not provide any information regarding the source of utilities for calculations of QALYs. Moore and colleagues (2005) constructed a Markov model to compare the cost-effectiveness of three regimens: standard therapy, addition of aprepitant to the standard regimen (strategy 1) and addition of aprepitant to the standard regimen if CINV (strategy 2) occurs. The analysis was conducted for five cycles of chemotherapy and the ICER was calculated to be $172,789 per QALY for strategy

1 and $160,236 per QALY for strategy 2. The authors concluded that use of aprepitant was not cost effective and should only be used in high-risk populations. Zbrozek and colleagues (Zbrozek et al., 1994) also reported high cost/QALY values for ondansetron compared to metoclopramide for prevention of acute CINV.

The high ICER for aprepitant in the previous two studies may be a function of employing the concept of QALYs for CINV, an acute condition with short term impact on quality of life and no proven impact on survival. Short term clinical outcome measures, for example complete protection from emesis, may prove to be better indicators to compare the cost-effectiveness of various antiemetic regimens. This is especially true until more robust methods are available to determine the utilities for acute conditions which are not shown to have a direct impact on survival of patients.

The previous economic evaluations (Ehlken et al., 2004; Moore et al., 2005) of the new antiemetic regimen were conducted from the payer perspective and thus did not include the indirect costs arising due to lost work productivity. The survey results from phase II of the study showed that uncontrolled emesis affects patients' ability to return to work and results in lost productivity. Previous studies have also published some information about the lost work productivity among patients and their caregivers (O'Brien et al., 1993). The addition of indirect costs led to an increase in the total costs associated with each of the four antiemetic regimens. However, the increase in the costs of regimen C was greater than that of regimen A which resulted in a decrease in the ICER of regimen A from 3,363.181 to $2,881.605 per patient with complete control of emesis. The study findings underscore the importance of controlling delayed emesis as it results in added costs. Regimen A provides better protection during delayed phase compared to regimen C, leading to reduced health care resource utilization which ultimately translates into better cost-effectiveness for regimen A. Additionally, the base case results show that compared to regimen D, the regimen A with aprepitant costs only an additional $154 to achieve complete control of emesis in one patient but provides better overall control of emesis. When the indirect costs are added to the direct costs, the difference in the total costs of achieving one patient with complete protection from emesis between the two regimens decreases to $52.

Previous antiemetic drug utilization studies (DURTO, 2003; Fabi et al., 2003) have reported the use of 5-HT_3RAs in the delayed phase even though there is insufficient evidence regarding its superiority compared to more traditional agents such as metoclopramide and

dexamethasone (IGAR, 1997; Latreille et al., 1998a). The effectiveness of regimen C (which includes metoclopramide in the delayed phase) had better efficacy in controlling emesis as compared to regimen D (the common antiemetic regimen used in clinical practice) but the efficacy became similar when the side effects of the regimen C are taken into consideration. However, the cost of achieving one patient with complete control of emesis is lower with regimen C. Thus, the model results provide additional evidence that use of 5-HT_3RA during the delayed phase does not result in a sufficient increase in effectiveness to offset the increase in costs.

For Moderately Emetogenic Chemotherapy Model

The decision model for prevention of CINV following administration of moderately emetogenic chemotherapy compared four antiemetic regimens, regimen 1 (only palonosetron), regimen 2 (only ondansetron), regimen 3 (combination of ondansetron and dexamethasone in the acute phase and dexamethasone in the delayed phase) and regimen 4 (combination of ondansetron and dexamethasone in acute and delayed phase). The base case results from the payer and societal perspectives showed that without considering the effectiveness, the cost associated with CINV and its treatment is highest for regimen 4 and lowest for regimen 3. In the cost-effectiveness analysis, regimen 2 was dominated by regimen 3 from both perspectives. From the payer perspective, the ICER for regimen 1 compared to regimen 3 was $3,582.48 and the ICER for regimen 4 compared to regimen 1 was $14,953.27 per patient with complete control of emesis. The ICER for regimen 1 compared to regimen 4 was $3,549.02 and the ICER for regimen 4 compared to regimen 1 was $6,499.87, from the societal perspective.

To our knowledge, only one study has conducted an economic evaluation of palonosetron compared to the older 5-HT_3RAs with and without the addition of dexamethasone (Vanscoy et al., 2004). There have been no published cost-effectiveness evaluations comparing palonosetron to other combination antiemetic regimens recommended for prevention of CINV following ME chemotherapy. Vanscoy and colleagues (Vanscoy et al., 2004) conducted a pharmacoeconomic evaluation of palonosetron in patients receiving moderately emetogenic chemotherapy. The outcomes and resource utilization for extreme events were compared for two groups of patients, one group receiving palonosetron and the other receiving either ondansetron, dolasetron or granisetron. The extreme event of CINV was defined as patients with severe nausea and two or

more emetic episodes on any day plus severe nausea on the following day, or patients with five emetic episodes on any day and moderate to severe nausea the following day. The study was conducted from the payer perspective and found that use of palonosetron resulted in a reduction in extreme events, which translates into significant savings for payers. However, the study did not examine the impact of CINV on emergency room visits, hospitalization costs or patient productivity. The current study results cannot be directly compared to results of this study as the latter does not report any cost-effectiveness ratios for the antiemetic regimens.

Previous economic evaluations have compared 5-HT_3RAs to the traditional antiemetic agents such as metoclopramide, or compared 5-HT_3RAs against one another for prevention of CINV due to moderately emetogenic chemotherapy (Cox & Hirsch, 1993; Kwong & Parasuraman, 1999; Lachaine & Laurier, 2002; Lachaine et al., 1999). Kwong and Parasuraman (Kwong & Parasuraman, 1999) reported that the cost of one additional effectively treated patient (no emesis and no adverse event for a three-day period) with ondansetron was $258 as compared to metoclopramide from a third-party payer perspective. However, as stated earlier, these results cannot be compared to the current study results because of differences in the treatment comparators, time horizon, and outcome measure.

One-way sensitivity analysis was conducted to identify key variables that may have an impact on the ICERs of the treatment regimens. The results very sensitive to changes in 1) the probability of no acute emesis, 2) the probability of no delayed emesis given no acute emesis, 3) the probability of receiving rescue medications in the acute phase given no acute emesis and 4) the probability of receiving rescue medications in the delayed phase given no delayed emesis. The variations in these parameters changed the dominance status and the ICERs of the individual antiemetic regimens. The ICER results were also sensitive to changes in the cost parameters. The ICER results showed that regimen 1 was dominated by regimen 3 when the cost of regimen 1 was increased by 20%, cost of regimen 4 was decreased by 20%, the cost of palonosetron was increased by 20% and the cost of ondansetron was decreased by 20%. A probabilistic sensitivity analysis was conducted to take into account all parameter variations simultaneously. This resulted in removal of regimen 1 from the ICER calculations due to extended dominance by a blend of regimen 3 and regimen 4. Compared to the base case estimates, the ICER of regimen 4 compared to regimen 3 decreased from $3,655.35 to $1,446.30 per patient with complete control

of emesis from the societal perspective. Thus, overall sensitivity analysis results show that the model estimates were very sensitive to variations in cost and efficacy parameters.

The sensitivity of the ICER results to changes in the parameter may be explained in part by the following. The calculation of the ICER for regimen 4 over regimen 3 resulted in $3,593.01 from payer perspective and $3,655.35 from the societal perspective. These ICER estimates for regimen 4 are very similar to the ICER estimates for regimen 1. Also, as mentioned earlier, regimens 1 and 4 have very similar effectiveness (0.695 and 0.699, respectively) and only differ in costs associated with CINV and its treatment. Thus, the economic evaluation of regimen 1 and 3 can be conducted using the cost-minimization method. However, due to the inclusion of both regimens in the model, and little differences in their effectiveness, the ICER results for the antiemetic regimens are very sensitive to any changes in the efficacy parameters. Additional analyses were conducted by removing regimen 4 from the decision model and the ICER for regimen 1 compared to regimen 3 was $3,682 per patient with complete control of emesis from the payer perspective and $3,233 per patient with complete control of emesis from the societal perspective. Probabilistic sensitivity analysis was also conducted for the new model with the three regimens. The ICER for regimen 1 compared to regimen 2 was approximately twice that obtained from the base case of the new model, however, the dominance status of the regimens remained the same.

Summary of Results for Phase I

When making treatment decisions, supportive care providers should select the most cost-effective treatment, bearing in mind that it may not be the least expensive. Even in a cost-sensitive managed care environment, the treatment with the lowest CE ratio may not always be the first choice. The definition of a cost-effective therapy should be based on the comparisons to the CE ratios of treatments for various diseases. In this case, it could be compared to other supportive care treatments for cancer. Although the threshold for determining whether an intervention is cost-effective is hard to define and generalize, less than $50,000 per life-year gained is generally considered acceptable for therapeutic interventions and more than $100,000 per life-year gained is generally considered excessive (Mark et al. 1995). Nevertheless, many interventions that cost as much as $100,000 per year of life saved have been accepted (Hillman and Kim, 1995). The interpretation of acceptable cost-effectiveness ratios usually depend on the individual decision makers and their budget constraints.

The available data do not allow direct comparisons of the CE ratios obtained in this study to those using life-years gained as effectiveness measures in the literature. Some studies have used life years gained while others have used quality adjusted life years gained. Even among economic evaluations that report cost per QALY, utilities from different sources have been applied (Ehlken et al., 2004; Moore et al., 2005; Zbrozek et al., 1994). All economic evaluations of antiemetic regimens employing utilities have reported very high cost per QALY estimates which fall above the acceptable cutoff of $100,000/QALY. Although, regimen C which includes metoclopramide in the delayed phase has the lowest cost per patient with complete control of emesis in patients receiving HE chemotherapy, it may not be the first choice of treatment by providers due to its side effects profile and multi dosing regimen per day. The ICER for the aprepitant regimen from payer perspective was calculated to be $3,363 per patient with complete control of emesis, which lies within the acceptable cutoff mentioned earlier. The sensitivity analysis results show that the ICER for regimen A remains below the acceptable threshold of $50,000 per QALY. Thus, it can be considered cost effective in preventing CINV for patients receiving highly emetogenic chemotherapy.

In addition to the economic factors, another factor that plays a role in selecting an intervention is patient preference. As indicated by the qualitative data from our survey results, almost 25% of patients preferred a single IV dose of palonosetron for prevention of CINV compared to the multi dosing regimen of other antiemetic drugs. Clinicians and health care providers will most likely take patient preference into consideration when choosing the optimal antiemetic intervention. However, patient preferences have not been incorporated in a quantifiable manner in the decision models. If patients show preference for single IV dose of palonosetron compared to a three-day regimen for prevention of CINV following ME chemotherapy, the ICER of the palonosetron regimen will be more cost-effective compared to other combination regimens.

The criteria for the effectiveness measure in clinical trials and economic evaluations for antiemetic agents are not explicitly established (Lachaine & Crott, 2003). In some previous economic evaluations the efficacy criteria adopted was complete control of emesis or both nausea and emesis (Ballatori et al., 1994) while in other studies lack of antiemetic side effects were also a criteria for efficacy (Kwong & Parasuraman, 1999). In the current study, for the HE chemotherapy model the base case analysis considered the control of emesis as the effectiveness

measure. However, scenario analysis was also conducted where the lack of side effects of regimen 4 was a criterion for effectiveness. Most of the previous economic evaluations were limited to the acute phase of CINV and underestimates the costs associated with CINV and its treatment. The previous evaluations were conducted to determine the cost-effectiveness of single drug antiemetic regimens with multi-dosing regimens which is no longer relevant. With the current guidelines and recommendations, combination regimens are the standard of practice and multi-dosing regimens are replaced by single dose administration. Thus, the current study provides economic results about the commonly employed antiemetic regimens in the recommended dosing schedule.

5.2: Review of Phase II Findings

Cost effectiveness analysis (CEA) and cost-utility analysis (CUA) are the most popular techniques used to conduct economic evaluation of healthcare interventions. These are most commonly employed to determine the incremental costs for receiving the incremental benefits, measured as clinical outcomes or life-years saved or QALYs gained. Although these methods provide helpful ways to determine cost-effective health care interventions, it is not feasible to employ them for acute conditions such as CINV where individuals experience the condition for a very short time period and may not be willing to forego future life years. In such scenarios, monetary valuation of benefits of the health care intervention may be more appropriate and can be used to determine the net benefit of the intervention. The net benefit values can be used to create a monetary rank order of disparate healthcare interventions for resource allocation using fixed budgets.

The primary goal of phase II was to determine the monetary value that patients with cancer place on improved emesis control. A contingent valuation survey was developed to measure patients' valuation of emesis control and data were collected by conducting face-to-face interviews with the study participants. This monetary value of benefits was then used to calculate the net benefit of the new antiemetic regimens compared to the standard regimen employed for prevention of CINV following HE and ME chemotherapy. The global perspective was used to develop the hypothetical scenarios for WTP estimation. The clinical, economic and quality of life outcomes associated with the antiemetic prophylaxis were explicitly presented to the respondents. Patients with cancer placed high importance on the risk reduction of acute and delayed emesis offered by the new antiemetic regimens. All 120 study participants preferred the

addition of aprepitant to the standard regimen compared to only the standard regimen. In the case of palonosetron, only one respondent preferred to receive the standard regimen due to dislike of injection and not enough emesis risk reduction for the palonosetron regimen. The WTP estimate was determined for the entire time period for which nausea and vomiting is associated with HE chemotherapy.

There have not been any published studies reporting the WTP for receiving a single IV dose of palonosetron instead of the standard regimen for prevention of CINV following ME chemotherapy. Our results showed that respondents were willing to pay on average $83.50 for a single dose regimen of palonosetron to receive a 12% reduction in delayed emesis. Approximately 91% of the study respondents were willing to pay for improved emesis control obtained due to the addition of aprepitant to the standard regimen for CINV due to HE chemotherapy. The WTP for improved emesis control due to the addition of aprepitant to a three-day regimen of a 5-HT_3RA and dexamethasone for each cycle of chemotherapy was found to be $89.90. This amount was for a 13% reduction in the incidence of acute emesis and 18% reduction in the incidence of delayed emesis following administration of HE chemotherapy.

The present study is the first to determine the monetary value of improved emesis control in the United States. A previous study conducted in Spain, Greece, Italy and Canada reported the monetary value that patients with cancer place on improved emesis control following cisplatin chemotherapy (Dranitsaris et al., 2001b). The study determined the maximum WTP separately for the acute and delayed phases of emesis. For a 10% improvement in acute emesis, a WTP in the range of $6-$54 per day was reported. Similarly for a 20% improvement in delayed emesis, a WTP in the range of $6-$45 per day for 4 days was reported. The study was conducted based on hypothetical benefits and not actual benefits of aprepitant as obtained from randomized clinical trials. Due to the differences in the methodology employed, our results could not be compared directly to those reported by Dranitsaris and colleagues. However, if the estimates from the previous study are used to estimate the maximum WTP for a period of three days, the results would be $8 for Greece, $70 for Italy, $114 for Canada, and $144 for Spain. The results of our study and the previous study (Dranitsaris et al., 2001b) show that patients' monetary valuation of benefit and quality of life are probably related to cultural differences and variations in the healthcare systems among the countries.

The qualitative data from the study participants showed that patients prefer the modest benefits offered by the new antiemetic regimens because nausea and vomiting affect their ability to return to work, ability to enjoy food, and their overall quality of life. Additionally, about one-fourth of the patients prefer palonosetron due to its single IV dosing regimen compared to the multi-day dosing pattern of the standard antiemetic regimen. However, in spite of what cancer patients reported about the importance of avoiding CINV, only about 6% of patients interviewed were willing to make out-of-pocket payments to cover the additional costs of the new drugs. It is suggested that this may be due to the fact that cancer patients face a number of chemotherapy-related complications such as hair loss, neutropenia, anemia mucositis etc, in which nausea and vomiting is only a part of the problem (Ortega, Dranitsaris, & Puodziunas, 1998). Ortega and colleagues reported similar results based on a WTP study which was conducted to estimate the monetary value of epoetin alfa for chemotherapy-induced anemia (Ortega et al., 1998). Only about 4% of cancer patients were willing to pay the actual costs of epoetin alfa for chemotherapy-induced anemia.

In the present study, WTP was measured using the ex-post or user based perspective. Neumann and Johannesson (1994) explored WTP for in vitro fertilization using both ex-post and ex-ante scenarios (Neumann & Johannesson, 1994). The study results showed that the implied WTP per baby is much higher for the insurance-based approach than the user-based approach. Hypothetically, user-based and insurance-based approaches should provide equivalent WTP but in general, since individuals are more risk averse about health care issues, the two methods results in different WTP. The method selected for determining WTP is important, since the insurance-based approach is expected to provide a higher mean WTP than the user-based approach (Gafni, 1996). In another study, the WTP estimates for benefits of epoetin alfa therapy obtained from the general population were higher compared to those obtained from cancer patients receiving chemotherapy (Ortega et al., 1998). Our study, which was conducted using user-based perspective among cancer patients, may have resulted in underestimation of the monetary value of the benefits of the new antiemetic regimens. The study, if conducted in the general population using the insurance-based perspective would be able to capture the non-user values or externalities associated with the use of antiemetic regimens.

The WTP survey included two scenarios: one for HE chemotherapy and one for ME chemotherapy. It is suggested that the WTP values offered for a question are partly determined

by the value provided for previous questions (Smith et al., 1999a). Thus, in this case it may result in order bias whereby the respondents may give WTP amounts for the second scenario based on those provided for the first scenario (Stewart, O'Shea, Donaldson, & Shackley, 2002; Venkatachalam, 2004). To avoid order bias, two versions of the survey were offered alternately to the respondents. Also, results of the bivariate statistical analyses showed that order in which the scenarios were presented did not bias the WTP values.

Many people are not willing to provide a monetary valuation for health gains because either they are opposed to paying for health or they oppose the suggestion of paying out of pocket (Smith, Olsen, & Harris, 1999d). The protest is usually expressed as zeroes or high WTP amounts. Smith and colleagues (Smith et al., 1999d) have recommended that WTP studies should report the proportion of zero responses and the protest bids. Individuals who oppose the valuation of health in monetary terms or think that they should not have to pay for health care intervention give a very high valuation or zeros for maximum WTP. These are called as protest bids. An assessment should be conducted to separate the genuine zeroes from the protest zeroes in the WTP study. In the current study, approximately 10% of the population reported zero bids as their WTP amounts. Out of these respondents, only about 2% were categorized as protest zeroes. A review of WTP literature showed that based on the format of the WTP question used in the study, the proportion of protestors ranged from 9.3% for the payment card method, 18.1% for the open ended format to 23.7% for the dichotomous choice method (Reaves, Kramer, & Holmes, 1999). The proportion of zero bids and protest zeroes in our study which employed the payment card method was either lower or comparable to the proportions reported in the literature (Donaldson, Thomas et al., 1997; Smith et al., 1999d). The lower proportion of zero bids for studies employing the payment card method may be because the payment card format may ease the valuation task faced by the survey respondents. Additionally, since the present data were collected using face-to-face interviews, participants had an opportunity to ask questions and clarify doubts.

Due to the hypothetical nature of contingent valuation studies, it is difficult to assess the validity of the WTP responses (O'Brien et al., 1998; Smith et al., 1999c). Ideally to establish criterion validity, one would compare the hypothetical values with actual observed market purchases. However, such a market does not exist for comparison and other methods need to be employed to determine the validity of the WTP results. One method suggested to assess the

construct validity of WTP responses is based on the premise that most goods and services have a positive income elasticity, i.e. higher incomes should be associated with higher WTP (Smith et al., 1999c). This theoretical construct can be tested by assessing the association of WTP amounts with respondents' income level (Neumann & Johannesson, 1994; Smith et al., 1999c). The theoretical validity of the study can also be assessed by regressing the WTP on a group of independent variables believed to be predictors of WTP (Neumann & Johannesson, 1994). The results of the semilogarithmic models for scenarios 1 and 2 showed the positive association of WTP amounts to the annual household income level of the respondents. The positive effect of income is consistent with the results of other WTP studies in the literature and establishes the construct validity of the survey results (Davey et al., 1998; Dranitsaris et al., 2001a).

Consistent with findings of a previous study (Dranitsaris et al., 2001a), clinical characteristics of the respondents, such as past experience of nausea and emesis did not have a significant influence on the WTP estimates for scenarios 1 and 2 . Though the multivariate results were not significant, it was found that patients who were chemotherapy naïve reported higher WTP compared to those who had received chemotherapy in the past but had not experienced CINV. The higher WTP amounts reported by chemotherapy naïve patients can be explained in part based on the patients' pre-treatment expectation of CINV. Previous research has shown that patients' pre-treatment expectation of nausea and emesis are significant predictor of CINV (Molassiotis et al., 2002; Montgomery et al., 1998; Roscoe et al., 2000). The patients may have pre-conceived expectancy regarding side effects of chemotherapy based on information either obtained from oncologists or nurses, or from their past experience with nausea and vomiting (may be due to pregnancy or motion sickness) or from other information sources such as television, friends and family (Roscoe et al., 2000). Thus chemotherapy naïve cancer patients may have pre-treatment expectations of experiencing side effects of chemotherapy which could have resulted in higher WTP amounts for the new regimen with a higher probability of preventing CINV.

In the present study, all respondents received a prophylactic antiemetic regimen for prevention of acute emesis following chemotherapy. Consistent with the results of a previous antiemetic drug utilization study (DURTO, 2003), the current study results showed that more than half of the respondents received the combination regimen of a 5-HT_3RA and dexamethasone for prevention of acute CINV. This regimen is consistent with the ASCO, NCCN and MASCC

recommended guidelines for prevention of CINV (R. J. Gralla et al., 1999; MASCC, 2004; NCCN, 2005). Since the respondents in our study were unable to provide complete information about the antiemetic regimens prescribed for prevention of delayed CINV, we could not determine its consistency with the recommended guidelines. The existing antiemetic regimens provide reasonably good protection against emesis but past studies have reported their inadequacy in controlling nausea (IGAR, 1995a, 2004; Molassiotis et al., 2002). This is reflected in the current study with approximately 44% of respondents experiencing nausea in spite of prophylactic antiemetic regimens. Past studies have shown that nausea is ranked as the most incapacitating side effects by cancer patients (Boer-Dennert et al., 1997; Griffin et al., 1996). It has been shown that nausea has a greater impact than vomiting on patient outcomes, overall functioning, emotional status, enjoyment of eating and quality of life (Foubert & Vaessen, 2005). Thus, there is need for more effective control of acute and delayed nausea following chemotherapy.

The WTP estimates obtained from the contingent valuation survey were used as the monetary valuation of benefits of the new antiemetic regimens for prevention of CINV and were used in cost-benefit analysis (CBA). The net cost of the new antiemetic regimens were calculated from the payer's perspective by subtracting the incremental benefits of the new regimen from the incremental costs due to the new regimen. If the value obtained is positive, it is termed as net costs and if the value obtained is negative, it is termed as net benefits. The addition of aprepitant to the standard regimen results in a net cost of $206.21 per chemotherapy cycle. On an average, patients with cancer received six cycles of chemotherapy resulting in additional costs of $1,237.26. Similarly, the incremental costs of using a single IV dose of palonosetron were higher than the incremental benefits, resulting in a net cost of $160.99 per chemotherapy cycle. The sensitivity analyses results showed that the incremental costs remained higher compared to incremental benefits when the cost of standard regimen for scenario 1 was increased. The high costs of the new antiemetic regimens were not justified by the benefits of the regimen as valued by the cancer patients receiving chemotherapy. This study is among the first to use CBA to conduct economic evaluation of antiemetic regimens for prevention of CINV. CBA has been used to determine the economic value of other supportive cancer care interventions, such as epoetin alfa for prevention of chemotherapy-induced anemia, amifostine for chemotherapy-induced toxicity (Dranitsaris, 1997; Ortega et al., 1998), comparing antineoplastic agents

(Dranitsaris, Elia-Pacitti, & Cottrell, 2004), and in the area of diabetes care (Davey et al., 1998; Dranitsaris, Longo, & Grossman, 2000).

5.3: Implications of Study Findings

The study results will be a valuable addition to the scientific literature in the field of supportive cancer care, pharmacoeconomics, and economic evaluation methodologies. In addition to its academic importance, the study results have implications for payers and clinicians.

Implications for Payers

The cost-effectiveness estimates for the prophylactic antiemetic regimens for prevention of CINV following HE and ME chemotherapy, obtained from the phase I of the study, has implications for third-party payers. The comparators in the decision model were based on the published guidelines, common regimens used in clinical practice and the addition of new antiemetic agents to the standard regimens. The dosage schedule and duration of therapy was also based on recommendations and clinical practice. Thus, the study attempted to provide cost effectiveness estimates for real-life use of antiemetic agents. The drug formulary administrators of managed care organizations can use the parameter estimates and the structure of the decision model to create budget impact models for their populations.

The costs associated with using 5-HT_3RA in the delayed phase (regimen 4) for prevention of CINV due to moderately emetogenic chemotherapy was higher as compared to the palonosetron regimen without any comparable increase in antiemetic effectiveness. This is consistent with previous results which report use of costly 5-HT_3RAs for delayed phase with no added benefits. Hospital and managed care organizations can promote the dissemination of the recommendations for appropriate antiemetic use so as to decrease costs without any impact on the benefits.

The monetary valuation of the improved emesis control provided by the two new antiemetic regimens allowed us to quantify the clinical, economic and humanistic outcomes associated with CINV and its treatment. This comprehensive evaluation of benefits using WTP estimates can be used to calculate the net benefits of prophylactic antiemetic regimens compared to other interventions, either other antiemetic regimens or other competing healthcare interventions. The WTP estimates used in CBA can be used by decision makers such as HMO

and drug formulary committees for resource allocation decisions. In a fixed budget scenario, a rank-ordering of the existing health care programs based on their net benefits can be done and compared with the net benefit of the new antiemetic regimen. This will help in reallocation of resources as interventions with smaller net benefits can be replaced with those regimens with higher net benefits.

Implications for Clinical Practice

The results from Phase II of the study suggest that control of nausea is not adequately achieved with the current antiemetic regimens and is an area for further research for pharmaceutical companies. The results obtained from Phase II also have implications for the oncologists and nurses. Patients place high importance on receiving even a modest improvement in the control of CINV. Nausea and vomiting is perceived by cancer patients to affect their quality of life, ability to eat and return to work. Oncologists and nurses should be cognizant of the level of importance that control of CINV has for patients so that they provide the best prophylactic treatment for prevention of CINV. In addition, there is a scope for improvement among clinicians with respect to adhering to the recommendations for utilization of the antiemetic agents.

5.4: Study Limitations

Both phases of the study have limitations and these are discussed below. These limitations need to be considered when deriving inferences from the reported results.

Limitations of Phase I

1. A decision model for economic evaluation is only as good as the data that is used to populate the model. An ideal data source would be a randomized, double-blind study examining the efficacy and the resource utilization associated with all the treatment alternatives. Since such a study is not available, cost and efficacy parameters were synthesized from a number of published studies and expert opinion. The impact of uncertainty in the parameter estimates on the results was evaluated by conducting sensitivity analysis.

2. The base case analysis assumes that the study populations in the source studies used for parameter estimates are comparable in their demographic and clinical characteristics. In

reality, this is possible only through randomization of the cohort to each treatment strategy included in the model. However, it is doubtful that such a randomized controlled clinical trial would be conducted in the near future.

3. In an attempt to balance a valid representation of the clinical path of CINV and its treatment and to keep the model transparent enough for the end-user to understand, a simple decision model was constructed. It was assumed in the base case that rescue medications were given for two days. It was also assumed that patients who receive rescue medications for breakthrough emesis and subsequently do not receive outpatient care were able to control their nausea and emesis and do not require any more medications. However, in clinical practice, patients may be switched to another rescue medication if the first agent does not work. Thus, the rescue medications may differ for each day during the delayed phase. It is difficult to decide on the sequence of the rescue medications and the level of control achieved by them.

4. The cost-effectiveness estimates of the antiemetic regimens are for a single cycle of chemotherapy and for chemotherapy naïve patients. The results cannot be generalizable for multiple cycles of chemotherapy or for patients who have previous chemotherapy experience.

5. It is reported widely that patient characteristics such as age and gender are associated with incidence of CINV. It would be useful to determine the ICER of the new antiemetic regimens in high-risk populations based on age and gender classification. However, the current decision model did not consider patient differences and their impact on ICER. This is due to lack of sufficient data regarding the efficacy and cost parameters in the different gender and age groups.

6. The indirect costs due to caregiver burden, requiring home help etc. due to uncontrolled delayed emesis were not included in the model. Also, the estimates for lost work productivity were based on one published study and future studies should collect primary information about work-days lost due to CINV.

Limitations of Phase II

7. The WTP survey was conducted among cancer patients receiving care at the Mary Babb Randolph Cancer Center in Morgantown, WV. The study population may not be representative of the general United States population and thus it limits the generalizability of the study results.

8. WTP estimates were obtained from the user-based perspective because the users are most familiar with the health outcomes being described. However, this may result in underestimation of the WTP for improved emesis control as it does not include the dollar valuation by the nonusers.

9. The contingent valuation method of estimating WTP for health benefits is associated with several biases, such as hypothetical bias and strategic bias. The validity of the WTP responses were established by determining the positive association of respondents' income to their WTP amounts. Strategic bias is said to exist when respondents deliberately give WTP amounts that differs from their true WTP. Although, respondents were instructed to imagine that their insurance does not pay for the drug, respondents know that in reality their insurance will pay for it and may thus provide higher WTP values.

10. Hypothetical bias is said to occur due to the hypothetical nature of the WTP question itself. In addition, the WTP amounts are based on stated preferences rather than observation of actual behavior. Thus, it difficult to validate the WTP results obtained using surveys by actual observation of the behavior in the market.

11. The payment card format of WTP elicitation is susceptible to range bias. In this study, we tried to minimize range bias by conducting a pilot study to determine the range for the final payment card and also instructed the respondents to give the exact WTP amount, if it is greater than the highest amount on the payment card. However, respondents may still be restricted in their responses based on the range provided.

5.5: Recommendations for Future Research

The economic evaluations in this study were conducted for a single cycle of chemotherapy. However, chemotherapy is administered for an average of 6 cycles and it is

important to demonstrate the cost-effectiveness of the antiemetic regimens over multiple cycles of chemotherapy. As mentioned earlier, the model is only as good as the data used to develop the model. The model should be populated with estimates of effectiveness and costs for each antiemetic regimen obtained from their use in clinical practice. Future economic evaluations should be conducted to determine the cost-effectiveness of the addition of aprepitant to a combination of palonosetron and dexamethasone for prevention of CINV due to highly emetogenic chemotherapy. Future research should be targeted at developing a decision model that incorporates compliance with antiemetic regimens, and patient preference for antiemetic agents to make it more relevant to clinical practice.

The contingent valuation study for determining WTP amounts for the aprepitant-based regimen and palonosetron should be conducted among the general population using the ex-ante perspective. This will provide the actual societal value of the new antiemetic regimens including the user, non-user and externality values. The externality values are obtained from a section of the general population who are not currently non-diseased and not at future risk but will be willing-to-pay for making the intervention available to the others. The WTP estimates thus obtained can be then utilized in CBA conducted form a societal perspective. In the US health care system, people make co-payments to receive health care services. Thus, WTP estimates for improved emesis control using increased co-payments as payment vehicle should be conducted in the United States general population. Such a study would allow us to compare the differences in WTP amounts for supportive cancer care such as prevention of CINV, based on the payment vehicle used.

5.6: Conclusions

The three-drug combination (regimen A) of aprepitant, a 5-HT_3RA and dexamethasone in the acute phase and aprepitant and dexamethasone in the delayed phase incurred the highest cost for prevention of CINV following highly emetogenic chemotherapy. The lowest cost for prevention of CINV following highly emetogenic chemotherapy was incurred by the combination regimen (regimen C) of a 5-HT_3RA and dexamethasone in the acute phase, and dexamethasone and metoclopramide in the delayed phase. When the side effects of regimen C were included in the model, it increased the costs incurred. The results showed that regimen A provided the highest effectiveness, i.e. patients with complete control of emesis. The combination regimen of 5-HT_3RA and dexamethasone in the acute and the delayed phase was dominated and not considered cost-effective.

For prevention of CINV due to moderately emetogenic chemotherapy, the costs were highest for the combination regimen of 5-HT_3RA and dexamethasone in the acute and the delayed phase (regimen 4), followed by the regimen with single dose of palonosetron (regimen 1), and followed by the regimen with a single dose of ondansetron (regimen 2). The least costs were incurred by the combination regimen (regimen 3) of 5-HT_3RA and dexamethasone in the acute and only dexamethasone in the delayed phase. The palonosetron regimen had similar effectiveness as regimen 4 and thus, the two regimens could be compared using cost-minimization analysis. The results could not be compared to any cutoff values to determine whether the regimens were cost-effective because there is no established criterion regarding cost for achieving one patient with complete control of emesis. If the current threshold for acceptable ICER values of intervention, i.e. below $50,000 per QALY is employed, the new regimens for prevention of CINV following chemotherapy would be considered as cost-effective.

The study results emphasizes that cancer patients receiving chemotherapy place a high level of importance in achieving better control of nausea and emesis. It also reiterates that uncontrolled CINV has a significant impact on patients' health-related quality of life (HRQOL). Although, based on the $50,000 per QALY threshold, the new regimens were considered cost-effective, the cost-benefit analysis results showed that the incremental costs of the new regimen exceeded the incremental benefits of the new regimens. However, in the present study the incremental benefits were from the patients' perspective and may be an underestimation of the societal benefits of the intervention. Future research should determine the willingness-to-pay for

improved emesis control from the general population so as to capture both the user and non-user values.

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APPENDIX I – Expert Panel Survey

1. In your practice, among 50 patients receiving single-day chemotherapy and prophylactic antiemetic medications, on an average, how many patients require intravenous infusion of saline or additional care by the oncologist/nurse during the first 24 hours?

2. Do you give prescriptions for rescue medications for delayed phase breakthrough emesis on the day of chemotherapy or when patients call up or comes in with uncontrolled CINV?

3. Please tell the most common rescue medications that you prescribe for breakthrough emesis during the acute and delayed phase?

4. Now please consider the 5 days following single-drug chemotherapy administration. In your practice, among 50 patients receiving chemotherapy, on an average, how many patients call up the oncologist/nurse for uncontrolled CINV?

5. On an average, how much time do you spend on the phone with the patient to enquire about CINV?

6. In your practice, among 50 patients receiving single-drug chemotherapy Out , on an average how many patients have to come back to the outpatient clinic for additional medical care (such as saline infusion and rescue antiemetic agents) for uncontrolled CINV?

APPENDIX II – Oncologist Script for Patient Recruitment

Hello Ms/Mr _____, I would like to talk to you about a study that a pharmacy student is doing as part of her Ph.D dissertation. She is conducting a study among patients at the cancer center to determine what it the value they place on certain new drug treatments available to prevent some side effects of chemotherapy. It will take about 20 minutes of your time. If you are interested in knowing more about the study and being a part of it I can introduce her to you.

APPENDIX III – Version A of the Willingness-To-Pay Survey

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING QUESTIONNAIRE

Interviewer:
Hello, I am Reema Mody, a PhD student in the School of Pharmacy at West Virginia University. Dr. _____ (name of the attending oncologist) should have explained briefly about the research study that I am conducting.
{Hand over the cover letter attached in the Section C of the protocol}
This is the information sheet that explains the study in detail. The interview has five sections and will take about 25-30 minutes to complete. We can go over the information letter together or you may read it and let me know if you have any questions regarding the study.
{After the participant finishes reading the cover letter}
Will you participate in the study?
{If No},
Thank you for your time.
{If Yes},
I would like to assure you that the information you provide would be kept strictly confidential. You are not required to give your name or any contact information. Your participation in the study is voluntary and you can withdraw from the study at any time. You do not have to answer any questions that may make you uncomfortable. The scenarios that I will describe in this study are entirely imaginary and have nothing to do with your condition. Your responses are valuable for this research and will increase the understanding of how patients with cancer value the benefits provided by different drugs to prevent nausea and vomiting due to chemotherapy.
May I begin the interview?

{If Yes}

"Before I ask you any questions, here is some information about cancer, chemotherapy and its related side effects. We can go over the material together".

*{Place **Insert A – Section1** in front of the participant and go over the material together}***.**

INSERT A

SECTION 1:Cancer, Chemotherapy and Nausea and Vomiting due to Chemotherapy

WHAT IS CANCER?

Cancer is a disease that affects various body tissues. If not treated, cancer can spread and can be fatal. But not everyone who gets cancer will die from it. As you know, cancer can be treated with surgery, radiation and chemotherapy. Our study focuses on two specific side effects of chemotherapy.

CHEMOTHERAPY AND ITS SIDE EFFECTS

Chemotherapy is the use of drugs to kill cancer cells. Chemotherapy is usually given in 4-6 cycles over a period of 4-6 months. But chemotherapy drugs may sometimes cause side effects. Nausea and vomiting are two side effects of chemotherapy. Nausea and vomiting due to chemotherapy is called Chemotherapy-induced Nausea and Vomiting (CINV). While these two side effects are not fatal, they can sometimes be so severe that some patients refuse further treatment for their cancer.

NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Nausea is having a sick feeling in the stomach, and vomiting is throwing up. Patients can experience both nausea and vomiting or each by itself. Nausea and vomiting can occur within 24 hours of chemotherapy and can last for 1 to 5 days after chemotherapy.

If nausea and vomiting are not prevented or controlled, it can sometimes lead to loss of appetite, loss of nutrients and electrolytes. Patients may not feel like doing anything, may not be able to cook and clean, and may not be able to go to work. Frequent vomiting can sometimes be dangerous because it can lead to loss of fluids from the body.

There are some drugs available to prevent nausea and vomiting due to chemotherapy. These drugs are to be taken before chemotherapy and for 3-4 days after chemotherapy.

Interviewer:
"Do you have any questions about this information?"

{If No},

"Since you have no questions about this section, we will go to the section 2 of this interview. Here I will be asking some questions about your past experiences with chemotherapy and nausea and vomiting associated with it".

If the participant has questions, answer their questions before moving to **Section 2**.

SECTION 2 - BACKGROUND INFORMATION

Interviewer will ask the following questions:

1. What type of cancer have you been diagnosed with? _____

2. Can you tell me which cycle of chemotherapy are you receiving today?

   □ Received in the last 3 months □ 1st cycle (never had chemotherapy)
   □ 1st cycle of new chemotherapy □ 2nd cycle □ 3rd cycle □ 4th cycle
   □ 5th cycle □ > 5th cycle

3. Chemotherapy regimen:

   _____
   _____

4. Antiemetic regimen:

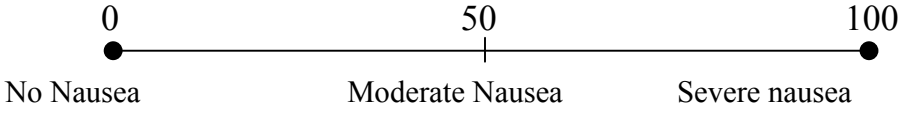
Prechemotherapy antiemetics	Postchemotherapy antiemetics
_____	_____
_____	_____

5. Did you experience nausea in the 4-5 days following your last chemotherapy cycle?

   □ Yes □ No□ Don't know

   If 'Yes', continue with Q6. If 'No' or 'Don't know', go to Q7.

6. *{Show the scale below to the participant}*
   Can you please mark X on this line to describe the severity of nausea that you experienced in the 4-5 days following your last chemotherapy cycle?



7. Did you experience vomiting episodes in the 4-5 days following your last chemotherapy cycle?

   □ Yes □ No □ Don't know

   If 'Yes', continue with Q8. If 'No' or 'Don't know', go to the next section.

8. Can you tell me on an average, how many episodes of vomiting you experienced per day during your last chemotherapy cycle? {E*xplain the meaning of episodes of vomiting as two bouts separated from each other by at least 1 minute}.*

   □ 1-2 episodes □ 3-5 episodes □ More than 5 episodes

{After completion of section 2}

Interviewer:

"Now, let's move on to the Section 3 of this interview. Here, I will be describing to you two scenarios about chemotherapy, nausea and vomiting, and its treatment. The scenarios are completely imaginary and does not relate to your condition. Dr. _____ (attending oncologist) may have discussed the course of treatment for your condition and the possible side effects with you. The scenarios that I am going to talk about are developed only for the purpose of this study".

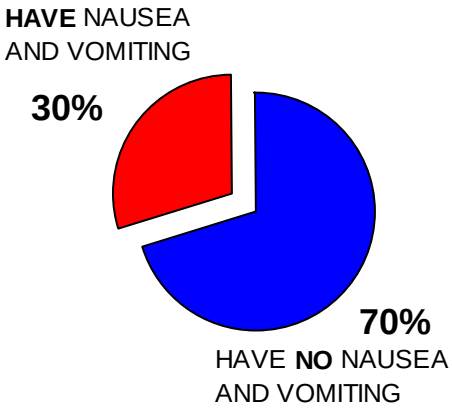
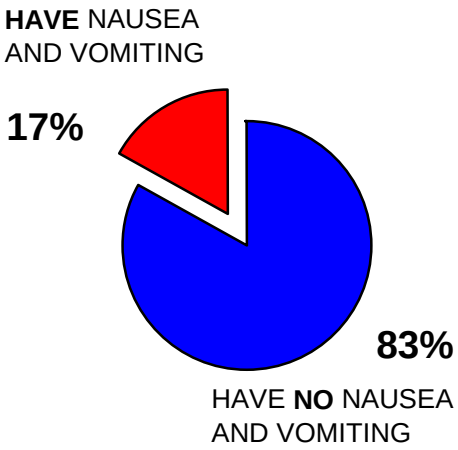
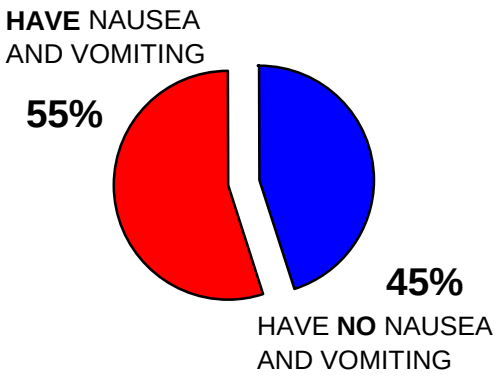
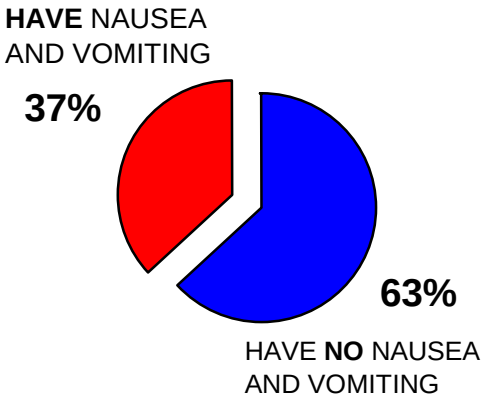
Interviewer:

"Imagine a scenario where the doctor has told you that you will be receiving certain chemotherapy drugs to treat cancer. As I mentioned earlier, the scenario is entirely imaginary".

"The doctor says that if drugs are not given to prevent nausea and vomiting, 99 out of 100 patients will experience nausea and vomiting within the first 24 hours of chemotherapy, and 75 out of 100 patients will experience nausea and vomiting for 3-4 days after chemotherapy. However, there are treatments available that can prevent nausea and vomiting due to chemotherapy".

"In this study we are considering two treatments that can prevent nausea and vomiting due to chemotherapy".

INSERT B

Treatment A	Treatment B (NEW DRUG + Treatment A)
Treatment A should be taken before chemotherapy and for 3 days after chemotherapy.	Treatment A should be taken before chemotherapy and for 3 days after chemotherapy. In addition, NEW DRUG is to be taken before chemotherapy and for 2 days after chemotherapy.
30 out of 100 patients will experience nausea and vomiting **within 24 hours** of chemotherapy 	**17 out of 100 patients** will experience nausea and vomiting **within 24 hours** of chemotherapy 
With Treatment A, 55 out of 100 patients will experience nausea and vomiting **for 3-4 days after chemotherapy** 	**With Treatment B, 37 out of 100** patients will experience nausea and vomiting **for 3-4 days after chemotherapy** 

{Show the **Insert B** and explain to the participant}

"Imagine that you are currently taking treatment A to prevent nausea and vomiting due to chemotherapy. This treatment has to be taken before chemotherapy and for three days after chemotherapy. Based on studies, out of 100 patients receiving Treatment A, 30 patients will have nausea and vomiting during 24 hours of chemotherapy.

"Now, imagine that there is another treatment B available, which is the addition of the new drug to the old treatment A. This new drug is to be taken in addition to the old treatment before chemotherapy and for two days after chemotherapy. Out of 100 patients receiving treatment B, 17 patients will have nausea and vomiting within 24 hours of chemotherapy. Thus, with the new treatment B, the chance of nausea and vomiting is reduced from 30% to 17%.

9. {Show the scale below to the respondent}
Indicate on this scale how important would it be for you to reduce your chance of having vomiting and nausea within the first 24 hours after chemotherapy from 30 in 100 to 17 in 100.
{Point out the appropriate pie charts on Insert B}

0	1	2	3	4	5	6	7	8	9	10
Not at all important					Somewhat important					Very important

"Now, with the old Treatment A, out of 100 patients who receive it, 55 patients will have nausea and vomiting for 3-4 days after chemotherapy. With the new treatment B, out of 100 patients who receive it, 37 patients will have nausea and vomiting for 3-4 days after chemotherapy. Thus, with the new treatment B, the chance of nausea and vomiting is reduced from 55% to 37%.

10. *{Show the scale below to the respondent}*
Indicate on the scale below how important would it be for you to **reduce your chance of vomiting and nausea for 3-4 days after chemotherapy from 55 in 100 to 37 in 100**.
{Point out the appropriate pie charts on Insert B}

0	1	2	3	4	5	6	7	8	9	10
Not at all important					Somewhat important					Very important

*Interviewer: **"**Assume that the two treatments cause similar side effects*.

11. Will you be willing to take the new drug along with treatment A if the new drug was available at no extra cost in preference to only treatment A?

    □ Yes □ No □ Don't know

    Please state reasons for your answer

    _____

    _____

Interviewer:
Assume that the two treatments cause similar side effects. But the new treatment B costs more than the old treatment A due to the addition of the new drug.

*One way of measuring the value of the **new drug** is to ask you how much money you would be willing to pay to receive the **new drug**.*

*Now imagine that your drug insurance plan **will not cover** the cost of the new drug. This means that you will have pay **extra out-of-pocket** for 3-day treatment, before chemotherapy and 2 days after chemotherapy, with the **new drug** for every cycle of chemotherapy. Now, this is simply a method of measuring the value you placed on the **new drug** and there is no right or wrong answer to this question.*

*Keeping in mind your own income level, thinking realistically about how much you can afford to pay, please look at this scale and indicate the **maximum amount** that you would be **willing to pay for new drug to be taken for 3 days**? Also please keep in mind that you have to pay this amount every month for 4 cycles in equal installments".*

12. Please state the **maximum amount** that you would be willing to pay for **new drug to be taken for 3 days**?

Put a **O** around the **maximum amount** that you are sure you would be prepared to pay.

$1.00

$1.50

$2.00

$2.50

$3.00

$4.00

$5.00

$6.00

$8.00

$10.00

$15.00

$20.00

$25.00

$30.00

$35.00

$45.00

$60.00

$75.00

$100.00

$125.00

$150.00

$200.00

$250.00

$300.00

$400.00

$500.00

$650.00

$800.00

$1,000.00

More than $1000 If more than $1,000, please specify the exact amount.

$_____

If the maximum WTP is $0, go to Q13. If the maximum WTP is any other value, go to the next section.

13. If the maximum WTP in Q12 is $0, please check one of the following options:

□ $0 is what it would be worth to me to prevent nausea and vomiting due to chemotherapy

□ People should not have to pay out of pocket for medication to prevent nausea and vomiting due to chemotherapy

□ I cannot afford to pay out of pocket for medications to prevent nausea and vomiting due to chemotherapy

□ I object the question

SCENARIO 2

Interviewer:

"Now, lets move on to Section 4 of this interview. Similar to the first scenario, the second scenario is also completely imaginary. The scenario that I am going to talk about is developed only for the purpose of this study.

"Imagine a scenario where the doctor has told you that you will be receiving certain chemotherapy drugs to treat the cancer. These drugs are different from the one described in the earlier scenario. The doctor says that if drugs are not given to prevent nausea and vomiting, approximately 60 patients will experience nausea and vomiting within the first 24 hours of chemotherapy, and 55 out of 100 patients will experience nausea and vomiting for 3-4 days after chemotherapy. However, there are treatments available that can prevent nausea and vomiting due to chemotherapy.

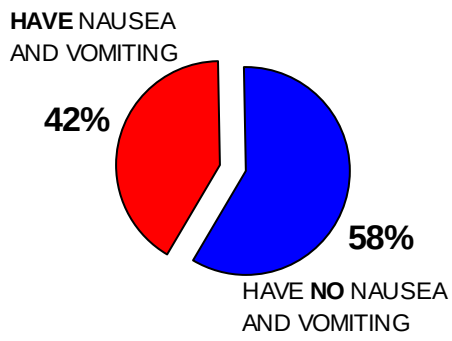
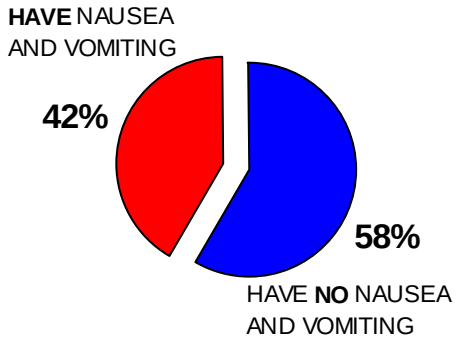
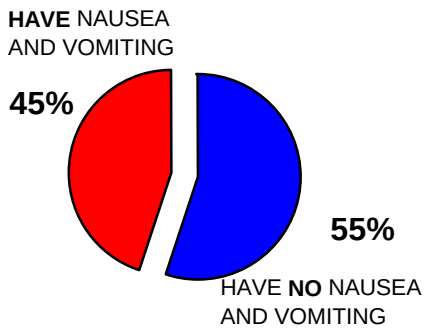
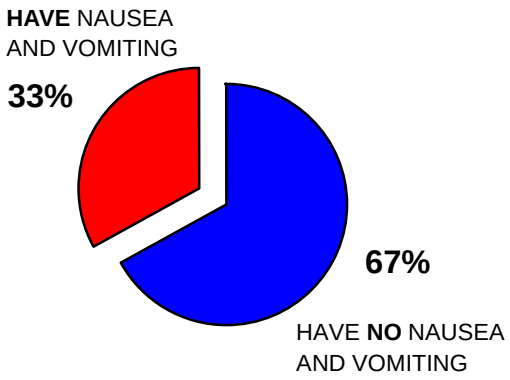
"In this study we are considering two treatments that can prevent nausea and vomiting due to chemotherapy".

{Show and explain **Insert C** to the participant}.

INSERT C

<table>
<tr><th>Treatment X</th><th>Treatment Y</th></tr>
<tr><td>Treatment X should be taken before chemotherapy and for 3 days after chemotherapy.

Treatment X is given as an injection before chemotherapy and is to be taken orally (by mouth) for the remaining 3 days after chemotherapy</td><td>Treatment Y should be taken before chemotherapy

Treatment Y is given as an injection before chemotherapy</td></tr>
<tr><td colspan="2">Treatment X and Treatment Y have similar chances of reducing nausea and vomiting within 24 hours of chemotherapy.</td></tr>
<tr><td>42 out of 100 patients will experience nausea and vomiting within 24 hours of chemotherapy
 
</td><td>42 out of 100 patients will experience nausea and vomiting within 24 hours of chemotherapy
 
</td></tr>
<tr><td>45 out of 100 patients will experience nausea and vomiting for 3-4 days after chemotherapy
 
</td><td>33 out of 100 patients will experience nausea and vomiting for 3-4 days after chemotherapy
 
</td></tr>
</table>

"Imagine that you are currently taking treatment X to prevent nausea and vomiting due to chemotherapy. This treatment has to be taken as an injection before chemotherapy and by mouth for three days after chemotherapy. Based on studies, out of 100 patients receiving Treatment A, 42 patients will have nausea and vomiting during 24 hours of chemotherapy.

"Now, imagine that there is a new treatment Y available, which is to be taken as an injection only before chemotherapy. Out of 100 patients receiving treatment B, 42 patients will have nausea and vomiting within 24 hours of chemotherapy. Thus, treatments X and Y have similar chances of preventing nausea and vomiting within 24 hours of chemotherapy".

"Now, with the old treatment X, out of 100 patients who receive it, 45 patients will have nausea and vomiting for 3-4 days after chemotherapy. With the new treatment Y, out of 100 patients who receive it, 33 patients will have nausea and vomiting for 3-4 days after chemotherapy. Thus, with the new treatment Y, the chance of nausea and vomiting is reduced from 45% to 33%.

14. *{Show the scale below to the respondent}*
Indicate on the scale below how important would it be for you to **reduce your chance of vomiting and nausea for 3-4 days after chemotherapy from 45 in 100 to 33 in 100**.
{Point out the appropriate pie charts on Insert C}

0	1	2	3	4	5	6	7	8	9	10
Not at all important					Somewhat important					Very important

{Keep the Insert C in front of the respondents}

Interviewer: *Assume that the two treatments cause similar side effects.*

15. Will you be willing to take the new drug Y if it is available at no extra cost in preference to treatment X?

□ Yes □ No □ Don't know

Please state reasons for your answer

_____

_____

Interviewer:
"Assume that the two treatments cause similar side effects. But the new treatment Y costs more than the old treatment X. One way of measuring the value of the **treatment Y** is to ask you how much money you would be willing to pay to receive **treatment Y**.

Now imagine that the cost of the new drug is **not covered** by your drug insurance plan. This means that you will have to **pay extra out-of-pocket** to receive **treatment Y for one day** for every chemotherapy cycle. Now, this is simply a method of measuring the **value** you placed on the **treatment Y**. There is no right or wrong answer to this question.

Keeping in mind your own income level, thinking realistically about how much you can afford to pay, please look at the scale and indicate the **maximum amount** that you would be **willing to pay to for treatment Y for one day**? Remember that you have to pay this amount for 4 chemotherapy cycles in equal installments".

16. Please state the **maximum amount** that you would be willing to pay for **new drug to be taken for 1 day**?

Put a **O** around the **maximum amount** that you are sure you would be prepared to pay.

$1.00
$1.50
$2.00
$2.50
$3.00
$4.00
$5.00
$6.00
$8.00
$10.00
$15.00
$20.00
$25.00
$30.00
$35.00
$45.00
$60.00
$75.00
$100.00
$125.00
$150.00
$200.00
$250.00
$300.00
$400.00
$500.00
$650.00
$800.00
$1,000.00
More than $1000

If more than $1,000, please specify the exact amount.
$_____

If the maximum WTP is $0, go to Q17. If the maximum WTP is any other value, go to Q18.

17. If the maximum WTP in Q17 is $0, please check one of the following options

□ $0 is what it would be worth to me to prevent nausea and vomiting due to chemotherapy

□ People should not have to pay out of pocket for medication to prevent nausea and vomiting due to chemotherapy

□ I cannot afford to pay out of pocket for medications to prevent nausea and vomiting due to chemotherapy

□ I object the question

Interviewer:
"Now I will be asking some questions about the level of difficulty you had in doing the interview"

18. *{Show the scale below to the participant}* On the scale shown, please indicate the level of difficulty you had in understanding the scenarios and the questions along with it.

0	1	2	3	4	5	6	7	8	9	10
Not at all difficult					Somewhat difficult					Extremely difficult

19. *{Show the scale below to the participant}* On the scale shown, please indicate the level of difficulty you had in answering the questions (Q.12 and Q. 16) on the maximum amount that you are willing to pay for the new drug and Treatment Y?

0	1	2	3	4	5	6	7	8	9	10
Not at all difficult					Somewhat difficult					Extremely difficult

*Interviewer: This is the last section of the interview and it related to (present the **Section 5** of the questionnaire) your background, such as age, race, education, employment, etc.*
{Read out the questions in Section 5}.

SECTION 5: DEMOGRAPHIC INFORMATION

{Interviewer will read the questions}

20. What is your age? _____ (years)

21. What is your gender? □ Male □ Female

22. What is your race?

□ Caucasians □ African American □ Asian □ Other (Please specify) _____

23. *{Show the question}* Please mark the highest level of education completed?

□ Never attended school □ Elementary school □ Some high school

□ High school graduate or GED □ Some college or technical school

□ College graduate □ Other (Please specify) _____

24. What is your marital status?

□ Married □ Single (Never married) □ Divorced

□ Widowed □ Living together (not married)

25. *{Show the question}* Which category best describes your employment status?

□ Full time worker (≥30 hours per week) □ Part time worker (< 30 hours per week)

□ Working at home □ Student □ Not working

26. *{Show the question}* Please indicate your approximate total annual household income.

□ ≤ $15,000 □ $15,001 - $30,000 □ $30,001 - $45,000 □ $45,001 - $60,000

□ $60,001 - $75,000 □ $75,001 - $100,000 □ > $100,000

27. Please state the number of members living in your household (Excluding yourself)

_____

28. *{Show the question}* What type of insurance do you have?

□ Private □ Medicare □ Medicaid □ Worker's compensation

□ HMO □ None □ Other (Please specify) _____

{After completion of Section 5} Record the time taken to complete the interview: _____

"Thank you so much for the time and effort you have taken to complete this interview. The information you have provided is valuable to this study. As a token of my appreciation, please accept this gift".

Curriculum Vitae

REEMA MODY, MBA, Ph.D.

OFFICE

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Waukegan, IL 60085
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PRESENT POSITION

12/2005 – Present Manager, Health Economics and Outcomes Research
TAP Pharmaceutical Products Inc. Lake Forest, IL 60045

EDUCATIONAL BACKGROUND

08/2000 – 12/2005 Doctoral Candidate, Department of Pharmaceutical Systems and Policy, West Virginia University, Major: Pharmacoeconomics & Health Outcomes Research.

06/1997 – 05/1999 Post Graduate Diploma in Pharmaceutical Management (MBA), SIES College of Management Studies, Mumbai, India.
Major: Pharmaceutical Marketing

06/1992 – 05/1996 B.S. in Pharmacy, University of Mumbai, Mumbai, India

PROFESSIONAL EXPERIENCE

01/2005 – 12/2005 Research Fellow, Department of Pharmaceutical Systems and Policy, West Virginia University. Funded by a research grant from MGI Pharma Ltd.

Dissertation: Economic evaluation of emerging antiemetic regimens to prevent chemotherapy-induced nausea and vomiting (CINV) following cancer chemotherapy. Major Advisor: Lesley-Ann Miller, Ph.D.

07/2001 – 12/2004 Research Fellow, Office of Drug Abuse Intervention Studies (ODAIS) affiliated with CDC-funded Prevention Research Center, West Virginia University.

Developed evaluation measures, performed data analysis, assisted in writing grants and manuscripts for evaluation of a school-based adolescent smoking cessation program sponsored by the American Lung Association

05/2003 – 08/2003 Outcomes Research Intern, Abbott Laboratories, Center for Pharmaceutical Appraisal & Outcomes Research, GPRD division

Development of a simulation model to evaluate the clinical and economic implications of noncompliance in patients with hypertension and conduct

sensitivity analysis to estimate the cost savings associated with increased compliance to antihypertensive regimen, and

Designed a Phase IV study for one of Abbott's marketed products incorporating health care resource utilization and general health status outcome measures

08/2000 – 06/2001 Graduate Teaching Assistant, School of Pharmacy, West Virginia University

07/1999 – 10/1999 Management Trainee, Product Management Team, Unichem Laboratories Ltd., Mumbai, India

06/1996 – 04/1997 Medical Sales Representative, Wockhardt Ltd., Mumbai, India

RESEARCH EXPERIENCE

09/2003 – 12/2005 Economic evaluation of emerging antiemetic regimens to prevent chemotherapy-induced nausea and vomiting (CINV) following cancer chemotherapy. Funded by a research grant from MGI Pharma Ltd.

Role: Principal Investigator

Currently working on dissertation project to determine the cost-benefit and cost-effectiveness of newly emerging antiemetic regimens to prevent CINV

02/2004 – 09/2004 Impact of cardiovascular comorbidity on overall and diabetes-related health care utilization and costs in type-2 diabetes patients. Funded by Takeda Pharmaceuticals North America, Inc.

Role: Research Assistant

Responsibilities included data analysis, generation of project report and publication of study results in peer-reviewed journals

08/2003 – 12/2003 Rates of hypertension-related medical and prescription utilization and costs in Medicaid population

Role: Principal Investigator

As part of course curriculum requirement, conducted descriptive analyses to determine the prevalence of hypertension and hypertension-related rates of healthcare utilization and costs based on demographic characteristics among WV Medicaid population

08/2003 – 12/2003 Economic evaluation of Aromatase inhibitors versus Tamoxifen in the first-line treatment of advanced breast cancer

Role: Principal Investigator

As part of course curriculum requirement, developed decision tree incorporating Markov model for determining cost-effectiveness of treatment strategies for advanced breast cancer

08/2002 – 09/2003 Developing a tool for assessing physicians' readiness to adhere with clinical practice guidelines for treatment of myocardial infarction patients. Funded by West Virginia University Senate Research Grant

Role: Research Assistant

Responsibilities included conducting phone interviews for survey item generation, developing survey instrument, and data analysis

RESEARCH PUBLICATIONS

Mody R, Smith M. Smoking status and health-related quality of life (HRQOL): Findings from the Behavioral Risk Factor Surveillance System (BRFSS) Data. *American Journal of Health Promotion* (In press)

Horn K, Dino G, Goldcamp J, Kalsekar I, ***Mody R***. The Impact of Not On Tobacco on teen smoking cessation: End-of-program evaluation results, 1998 to 2003. *Journal of Adolescent Research.* 2005 Nov; 20(6): 640-661

Mody R, Miller LAN. Confounding factors affecting association of antihypertensive medications and pulse pressure (Letter), *American Journal of Medicine*. 2004 Nov 1;117(9):709-10

Amonkar M, ***Mody R***. Developing profiles of postmenopausal women being prescribed estrogen therapy to prevent osteoporosis. *Journal of Community Health.* 2002 Oct;27(5):335-350

Hassan M, Kalsekar I, Madhavan S, ***Mody R***, Amonkar M. Determinants of readiness to quit smoking among women of childbearing age. *Journal of the American Medical Women's Association* (Under review)

Mody R, Kalsekar I, Kavookjian J, Iyer S, Rajagopalan R, Pawar V. Economic impact of cardiovascular co-morbidity in patients with type 2 diabetes. *Journal of Diabetes and Its Complications* (Under review)

Kalsekar I, Iyer S, ***Mody R,*** Rajagopalan R, Kavookjian J. Economic consequences of choice of diabetes therapy in a Medicaid population. *Journal of Managed Care Pharmacy* (Under review)

SELECTED RESEARCH PRESENTATIONS

Mody R, Miller LAN. Willingness-to pay for antiemetic regimens for prevention of chemotherapy-induced nausea and vomiting. Accepted as a poster presentation at the 27th Annual Meeting of the Society for Medical Decision Making, San Francisco, CA, October 2005

Mody R, Kalsekar I, Kavookjian J, Iyer S, Rajagopalan R, Pawar V. Economic impact of cardiovascular co-morbidity in patients with type 2 diabetes. Presented as a poster at the ISPOR 10th Annual International Meeting, Washington DC, May 2005

Kavookjian J, ***Mody R,*** Kalsekar I, Iyer S, Rajagopalan R, Pawar V. Prevalence of co-morbid conditions and concomitant medication use among type 2 diabetes patients in a state Medicaid population. Presented as a poster at the ISPOR 10th Annual International Meeting, Washington DC, May 2005

Kalsekar I, Iyer S, ***Mody R,*** Rajagopalan R, Kavookjian J. Economic consequences of choice of diabetes therapy in a Medicaid population. Oral presentation at the ISPOR 10th Annual International Meeting, Washington DC, May 2005

Mody R, Smith M. Rates of hypertension-related medical and prescription utilization and costs in a state Medicaid population. Presented at the Drug Information Association (DIA) Meeting, Washington D.C., June 2004

Miller LAN, ***Mody R***, Singer ME. Understanding the characteristics of non-traders in TTO utility elicitation. Oral presentation at the ISPOR 9th Annual International Meeting, Arlington, VA, May 2004

Miller LAN, ***Mody R*** (Presenting Author). A descriptive analysis to investigate the differences between traders and non-traders in time trade off. Presented as a poster at the ISPOR 9th Annual International Meeting, Arlington, VA, May 2004

Mody R, Smith M. Smoking Status and health-related quality of life (HRQOL): Findings from the Behavioral Risk Factor Surveillance System (BRFSS) Data. Oral presentation at the ISPOR 8th Annual International Meeting, Arlington, VA, May 2003

Mody R, Kavookjian J, Kamat S, Coffindaffer J. Assessing physician's barriers to adherence with clinical practice guidelines for prescribing beta-blockers in post myocardial infarction patients. Presented as a poster at the Annual American Pharmaceutical Association Meeting, New Orleans, March 2003

RELEVANT GRADUATE COURSES

Basic Econometrics
Pharmacoeconomics
Decision Analysis in Healthcare
Outcomes Research and Quality of Life Assessment
Epidemiology
Pharmacoepidemiology
Research Methods
Survey Research
Data Management and Analyses
Social and Behavioral Theory
Principles of Marketing
Consumer Behavior

PROFESSIONAL DEVELOPMENT

10/2005	SMDM Annual Meeting
	Courses:Probabilistic Cost-Effectiveness Modeling
07/2004	Graduate Summer Institute of Epidemiology and Biostatistics, Johns Hopkins School of Public Health
	Courses: Multilevel Models, Statistical Analysis for Cohort Study Designs
05/2004	ISPOR International Annual Meeting
	Courses: Old and new utility measures in health economics and outcomes research, Reed Johnson & Brett Hauber
05/2003	ISPOR International Annual Meeting
	Courses: Quality of Life – Advanced Course**,** Karen Gold

COMPUTER SKILLS

Statistical packages: SPSS, STATA, FoxPro, SAS

Decision Analysis software: DATA TreeAge, @RISK, Precision Tree

HONORS AND AFFILIATIONS

2004: Student Poster Award – 1st place, Drug Information Association (DIA) 40th Annual Meeting

2004: Graduate Research Award, School of Pharmacy, West Virginia University

2003: Best Student Podium Award, ISPOR 8th Annual International Meeting

2003-2004: Vice-President of the West Virginia ISPOR Student Chapter

2005-Present: Member, Society of Medical Decision Making (SMDM)

2001-Present: Member, International Society for Pharmacoeconomics & Outcomes Research (ISPOR)

REVIEWER

Preventive Medicine

Contributed Research Abstract Review Committee for 8th Annual meeting of ISPOR