

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**THE USE OF APREPITANT FOR THE  
PREVENTION OF CHEMOTHERAPY INDUCED  
NAUSEA AND VOMITING**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**March 2009**



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## CONTENTS

ABOUT THIS REPORT .....	4
SUMMARY .....	5
BACKGROUND.....	6
CURRENT GUIDANCE.....	8
APREPITANT.....	8
EFFICACY.....	8
HIGHLY EMETOGENIC CHEMOTHERAPY (HEC).....	8
MODERATELY EMETOGENIC CHEMOTHERAPY (MEC) .....	12
ADVERSE EFFECTS .....	14
HIGHLY EMETOGENIC CHEMOTHERAPY.....	14
MODERATELY EMETOGENIC CHEMOTHERAPY .....	15
MULTIPLE CYCLES OF CHEMOTHERAPY .....	15
DOSAGE, ADMINISTRATION AND COST.....	15
PLACE IN THERAPY.....	16
ARRANGEMENTS FOR PRESCRIBING.....	17
FUTURE DEVELOPMENTS .....	18
ACKNOWLEDGEMENTS .....	18
REFERENCES .....	19
APPENDICES .....	21
TABLE 12. EMETOGENIC POTENTIAL OF SOME ANTINEOPLASTIC AGENTS .....	21

**ABOUT THIS REPORT**

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<b>Subject</b>	<b>Date issued</b>
Current therapeutic strategies for pulmonary arterial hypertension	March 2009
The use of lapatinib in the management of metastatic breast cancer <b>(N)</b>	November 2008
The use of liposomal doxorubicin in the management of metastatic breast cancer	October 2008
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer	September 2007
The use of entecavir in the management of chronic hepatitis B infection <b>(N)</b>	March 2007
The use of natalizumab in the management of multiple sclerosis <b>(N)</b>	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer <b>(N)</b>	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma <b>(N)</b>	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer <b>(N)</b>	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma <b>(N)</b>	February 2006

*Older reports are available via our website or on request*

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

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## SUMMARY

- Chemotherapy-induced nausea and vomiting (CINV) is an important adverse effect to control in cancer patients. It can significantly impair a patient's quality of life and may result in refusal of treatment. CINV can be categorised as acute (nausea and vomiting in the first 24 hours following chemotherapy), delayed (occurring 24 or more hours after chemotherapy) or anticipatory (occurring prior to chemotherapy).
- Highly emetogenic chemotherapy agents (HEC) are likely to cause emesis in over 90% of patients in the absence of antiemetic prophylaxis. Moderately emetogenic chemotherapy agents (MEC) are likely to cause emesis in 30- 90% of patients.
- Aprepitant is a highly-selective antagonist of substance P at neurokinin (NK<sub>1</sub>) receptors licensed as part of a combination therapy regimen that includes a corticosteroid and a 5-HT<sub>3</sub> antagonist for the prevention of acute and delayed nausea and vomiting associated with cisplatin based HEC, and the prevention of nausea and vomiting associated with MEC.
- The efficacy and safety of aprepitant in combination with ondansetron and dexamethasone for the prevention of CINV in patients receiving cisplatin based HEC has been evaluated in three RCTs. The addition of aprepitant resulted in statistically significant improvements in complete response during the acute, delayed and overall phase compared to ondansetron and dexamethasone alone. All three studies reported a significant reduction in favour of aprepitant in the number of patients with emesis, but aprepitant did not consistently reduce nausea.
- One RCT evaluated the efficacy and safety of aprepitant for the prevention of CINV in patients receiving MEC. The number of patients with a complete response was statistically significantly higher in the aprepitant group in the acute and overall phases, but not in the delayed phase. Patients receiving aprepitant experienced fewer episodes of emesis overall, but there was no difference in the number of patients who experienced no nausea overall.
- The most common reported adverse events with the aprepitant regimen in patients receiving HEC were nausea, asthenia and fatigue. In patients receiving MEC only fatigue was reported more frequently with aprepitant.
- Aprepitant is expected to be reserved for use in combination with a 5-HT<sub>3</sub> antagonist and dexamethasone for the prevention of CINV due to HEC in patients considered to be at high risk, and in those who have experienced emesis despite treatment with a combination of an 5-HT<sub>3</sub> antagonist and dexamethasone in a previous cycle of HEC. Aprepitant has not been shown to be cost effective in patients receiving MEC.
- At a cost of £47.42 per patient, the addition of aprepitant to a standard regimen including a corticosteroid and a 5-HT<sub>3</sub> antagonist will more than double the cost of antiemetic therapy, although this may be partially offset by some reduction in the need for rescue therapy.

## BACKGROUND

It is important to control chemotherapy-induced nausea and vomiting (CINV) in cancer patients because it is one of the most feared side effects of chemotherapy.<sup>1,2</sup> It is a significant side effect experienced by many cancer patients, and can impair patients' quality of life and in serious cases, cause dehydration, metabolic disturbances, anorexia and malnutrition.<sup>2,3</sup> This can potentially lead to a patient's refusal to continue with the most effective treatment.<sup>2</sup> Chemotherapy-related emesis has been reported in around 70% to 80% of cancer patients, therefore effective control of CINV is a critical aspect of overall patient care.<sup>3</sup>

CINV can be categorised in three ways:<sup>3,4</sup>

1. 'Acute' – where nausea and vomiting occur within the first 24 hours after chemotherapy has started
2. 'Delayed' – vomiting occurring 24 hours after treatment and up to 120 hours after chemotherapy
3. 'Anticipatory' – a learned or conditional response that occurs in patients who have had poorly controlled CINV during a previous course of chemotherapy

It is essential to control nausea and vomiting in the acute period because failure to control CINV in the acute phase is highly predictive for delayed emesis in the same cycle.<sup>2,5</sup> Delayed vomiting is difficult to treat and is associated with an increased likelihood of acute and delayed emesis in future cycles.<sup>2</sup>

Antineoplastic agents can be classified according to their potential for emetogenicity.<sup>6</sup> A highly emetogenic agent (e.g. cisplatin  $\geq 50$  mg/m<sup>2</sup>) is likely to cause emesis in over 90% of patients in the absence of effective antiemetic prophylaxis.<sup>6</sup> A moderately emetogenic agent (e.g. cyclophosphamide  $\leq 1,500$  mg/m<sup>2</sup>) is likely to cause emesis in 30 – 90% of patients in the absence of antiemetic prophylaxis.<sup>6</sup> In contrast, minimally emetic agents (e.g. fludarabine or rituximab) are likely to cause emesis in less than 10% of patients.<sup>6</sup> It is possible that when agents are combined, the effects may be additive or synergistic. A summary of the emetogenic potential of various chemotherapy agents is presented in table 12. In addition to the type of chemotherapeutic agent, certain patient-specific risk factors are known to increase the risk for developing CINV.<sup>2</sup> They include age < 50 years, patients with pre-existing nausea and those who experienced previous CINV. Gender also plays a role, with women more likely to experience CINV than men. This review covers CINV due to highly and moderately emetogenic chemotherapy agents only.

The precise mechanisms by which chemotherapy induces CINV are largely unknown. However, it appears that these agents cause nausea and vomiting by action at various sites, and that some act at multiple sites.<sup>7</sup> For most agents, the most common mechanism is thought to be activation of the vomiting centre and chemoreceptor trigger zone (CTZ).<sup>7,8</sup> Chemotherapeutic agents appear to facilitate the release of various neurotransmitters which initiate the emetic reflex by stimulating serotonin (5-HT<sub>3</sub>), neurokinin (NK<sub>1</sub>) and dopamine (D<sub>2</sub>) receptors.<sup>8</sup>

The prevention and treatment of CINV involves the use of corticosteroids, 5-HT<sub>3</sub> receptor antagonists, dopamine D2 antagonists, and more recently NK<sub>1</sub> receptor antagonists.<sup>3,9</sup> The level of antiemetic therapy offered should be appropriate for the potential emetogenicity of the chemotherapy regimen being used and the patients individual risk factor. For antiemetics given up to an hour prior to chemotherapy the oral route is the preferred method of administration.<sup>6,10-12</sup> Intravenous agents are available for those patients who are unable to take oral agents.<sup>6,10-12</sup> Optimal emetic control in the acute phase is essential to prevent CINV in the delayed phase.<sup>11,12</sup>

There are no nationally accepted guidelines for the prevention and treatment of CINV. However, various network guidelines are in use based mostly on the American Society of Clinical Oncology (ASCO) guidelines for antiemetics in oncology,<sup>13</sup> with local variations in the duration and dose of 5-HT<sub>3</sub> and steroid cover.<sup>10-12,14,15</sup> A combination of a 5-HT<sub>3</sub> receptor antagonists and a corticosteroid administered prior to chemotherapy, followed by administration of one or both agents for several days is typically used for the prevention for CINV after moderate to highly emetogenic chemotherapy regimens.<sup>4,11,12</sup> 5-HT<sub>3</sub> receptor antagonists are considered to be equally effective, although ondansetron appears to be the most commonly used in practice.<sup>4,11,12</sup> Dexamethasone is the most widely used corticosteroid for CINV, but is not required when steroids are included in a chemotherapy regimen. Breakthrough nausea and vomiting can still occur despite prophylaxis and requires additional therapy. Typical antiemetic regimens for the prevention and treatment of CINV are shown in table 1.

**Table 1. Antiemetic regimens for the prevention and treatment of CINV.**<sup>10-12,14,15</sup>

<b>Moderately emetogenic chemotherapy</b>	
<b>Pre-medication</b>	<b>Take home medication</b>
Dexamethasone 4-8mg oral or IV	Dexamethasone 8mg oral for 2-4 days
5-HT <sub>3</sub> receptor antagonist 8mg oral or IV	Metoclopramide 10-20mg TDS-QDS oral (or domperidone 20mg TDS) for 3-4 days when required
<b>Highly emetogenic chemotherapy</b>	
<b>Pre-medication</b>	<b>Take home medication</b>
Dexamethasone 4-8mg oral or IV	Dexamethasone 8mg for 2-4 days
5-HT <sub>3</sub> receptor antagonist 8mg oral or IV	5-HT <sub>3</sub> receptor antagonist 8mg BD for 2-3 days
	Metoclopramide 10-20mg TDS-QDS oral (or domperidone 20mg TDS) for 3-4 days when required

## **CURRENT GUIDANCE**

The National Institute for Health and Clinical Excellence (NICE) has not issued guidance for CINV or the use of aprepitant. In November 2004, the Scottish Medicines Consortium (SMC) accepted aprepitant *'for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin based chemotherapy.'*<sup>16</sup> However, in February 2006, the SMC decided: *'Aprepitant as part of combination therapy is not recommended for use within NHS Scotland for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy.'* The reason for this decision was that the economic case for use in this indication had not been demonstrated.<sup>17</sup>

## **APREPITANT**

Aprepitant (Emend<sup>®</sup>, MSD Ltd) is the first in a new class of oral antiemetic agents.<sup>18</sup> It is a highly-selective antagonist of substance P at neurokinin (NK<sub>1</sub>) receptors, with little or no affinity for serotonin, dopamine or corticosteroid receptors.<sup>9,18</sup> Substance P, a neuropeptide of the tachykinin family, which itself is able to induce emesis, is distributed widely and abundantly in the mammalian central nervous system and other tissues.<sup>9,18</sup> NK<sub>1</sub> receptors are present in the brain stem emetic centre and gastrointestinal tract, and specific blockade of these receptors provides a novel mechanism of action for prevention of induced nausea and vomiting.<sup>9</sup>

Aprepitant is licensed as part of a combination therapy regimen that includes a corticosteroid and a 5-HT<sub>3</sub> antagonist:<sup>18</sup>

1. For the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin based chemotherapy in adults.
2. For the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

The purpose of this report is to evaluate the efficacy and safety of aprepitant in the treatment of cancer chemotherapy induced nausea and vomiting (CINV).

## **EFFICACY**

### **HIGHLY EMETOGENIC CHEMOTHERAPY (HEC)**

The efficacy and safety of aprepitant in combination with ondansetron and dexamethasone for the prevention of CINV in patients receiving cisplatin based HEC has been evaluated in three multi-centre, randomised, double-blind, parallel group studies: protocol 052 (n = 530),<sup>19</sup> 054 (n = 569)<sup>20</sup> and 801 (n = 489).<sup>21</sup> Although there are some outcome data available beyond cycle one, all three studies of HEC were designed to evaluate the efficacy of aprepitant only for the initial cycle of chemotherapy. Studies 052 and 054 upon which the license for HEC is based were of identical design to allow for subsequent pooling of the data for analysis.<sup>9,22</sup> The pooled results are discussed in the text below (details of the individual trials are presented in

Appendix 2). Study 801 differed from 052 and 054 in that ondansetron was used from day two to four of the standard regimen arm.<sup>21</sup>

Cisplatin naïve patients with solid tumours who were scheduled to receive their first chemotherapy cycle including cisplatin  $\geq 70$  mg/m<sup>2</sup> were enrolled into these three trials. Patients were stratified according to the emetogenic chemotherapy received and were randomised to either the aprepitant or standard therapy regimen. Matching dexamethasone and aprepitant placebos were given to maintain blinding. As pharmacokinetic studies in healthy subjects showed that aprepitant increased plasma dexamethasone levels approximately two fold, the dose of dexamethasone was reduced in the aprepitant regimen to ensure similar plasma levels between the treatment groups. The medication regimens used in the three studies is detailed in table 2.

The primary end point in all three studies was the proportion of patients achieving a complete response (CR), defined as no emesis and no use of rescue therapy for treatment of either nausea or emesis, in the five day study period following initiation of cisplatin chemotherapy in cycle one. Patients used a diary to record the occurrence of emetic episodes or retching, the use of rescue therapy, and daily nausea severity ratings (using a validated 100 mm visual analogue scale [VAS]). In studies 052 and 054 patients also completed a Functional Living Index Emesis (FLIE) questionnaire on day six, which captured information about the effect of CINV on patients' daily lives. Secondary end points in all studies included; CR in the acute phase (0 to 24 h after cisplatin), CR in the delayed phase (days 2 to 5 after cisplatin), no emesis, no significant nausea (VAS score < 25 mm), and in studies 052 and 054 only, complete protection (no emesis, no rescue therapy and no significant nausea, VAS score < 25 mm), and total control (no emesis, no rescue therapy and no nausea, VAS score < 5 mm). The endpoints and definitions are consistent with current medical literature recommendations for antiemetic trials. CR is considered a highly accurate and reliable measure for evaluating anti emetic regimens in CINV, and correlates with patients' perception of emesis. The update committee of the American Society of Clinical Oncology (ASCO) recommends the use of CR for the guideline development process, and that the assessment of vomiting and nausea for five days after treatment should be standard primary end points for clinical trials of antiemetics in oncology.<sup>13</sup>

**Table 2. Medication regimens by study.**<sup>19-21</sup>

Study	Day one		Days two to three		Day four	
	APR	Standard regimen	APR	Standard regimen	APR	Standard regimen
052 054	APR 125mg Ond 32mg Dex 12mg	Ond 32mg Dex 20mg	APR 80mg Dex 8mg both OD	Dex 8mg BD	Dex 8mg OD	Dex 8mg BD
801	APR 125mg Ond 32mg Dex 12mg	Ond 32mg Dex 20mg	APR 80mg Dex 8mg both OD	Ond 8mg Dex 8mg both BD	Dex 8mg OD	Ond 8mg Dex 8mg both BD

APR=aprepitant (oral), Dex=dexamethasone (oral), and Ond=ondansetron (intravenously).

In the pooled data from studies 052 and 054, a modified intention to treat (ITT) approach was used for the primary analysis, which included all patients who received cisplatin, took study drug and had at least one post treatment assessment (n = 1,043 (aprepitant n = 520, control n = 523)). The individual studies had 90% power to detect a 15% difference in CR rates overall, based on a two sided test at a significance level  $\alpha = 0.05$ , with a sample size of 235 evaluable patients per treatment group. The baseline characteristics of the randomised study groups were well matched with respect to demographics, type of malignancy and chemotherapeutic regimens.

With respect to the primary end point, over the entire five day study period significantly more patients in the aprepitant group achieved a CR compared to the control regimen (absolute difference 19.9%).<sup>9,22</sup> This equates to a number needed to treat of six (NNT = 6, i.e. six patients need to be treated with aprepitant for one to experience a CR). The aprepitant containing regimen was also significantly more effective than the control regimen in achieving a CR in the acute phase (absolute difference 12.7%, NNT = 8) and the delayed phase (absolute difference 20.3%, NNT = 5). The pooled results for CR in all phases are shown below in Table 3.

**Table 3. Pooled analyses of complete response rates (052 and 054).**<sup>9,22</sup>

Phase	Aprepitant (n = 520)	Control (n = 523)	Difference (95% CI*)	p- value
<b>Overall</b> (primary endpoint)	67.7%	47.8%	19.9% (14.0 to 25.8%)	< 0.001
<b>Acute</b>	86.0%	73.2%	12.7% (7.9 to 17.6%)	< 0.001
<b>Delayed</b>	71.5%	51.2%	20.3% (14.5 to 26.1%)	< 0.001

\*CI: confidence interval

The pooled results for secondary efficacy end points are shown below in table 4. The percentage of patients in the aprepitant group with no emesis was significantly higher than the control group, in all three phases (all  $p < 0.0001$ ). For the endpoint of no nausea, the aprepitant regimen was significantly superior to the control regimen in the overall ( $p < 0.05$ ) and delayed phases ( $p < 0.01$ ), but not the acute phase. Aprepitant was significantly superior to the control regimen for the endpoint of no significant nausea in the overall ( $p < 0.05$ ), delayed ( $p < 0.05$ ), and acute phases ( $p < 0.01$ ). Similarly, the number of patients experiencing complete protection (no emesis, no rescue, and no significant nausea) was significantly higher in the aprepitant group in all three phases ( $p < 0.001$ ). Based in the FLIE total score, significantly more patients in the aprepitant group reported minimal or no impact of CINV on the daily life than the control group (absolute difference 10%,  $p < 0.01$ , NNT = 10).

**Table 4. Pooled analyses of secondary efficacy endpoints.<sup>22</sup>**

Endpoint	Phase	Aprepitant (n = 520)	Control (n = 523)	p-value
No emesis	Overall	72%	50%	< 0.01
	Acute	87%	74%	< 0.01
	Delayed	76%	54%	< 0.01
Complete protection	Overall	60%	45%	< 0.01
	Acute	82%	70%	< 0.01
	Delayed	64%	48%	< 0.01
No nausea	Overall	48%	42%	< 0.05
	Acute	70%	68%	NS*
	Delayed	52%	44%	< 0.01
No significant nausea	Overall	72%	65%	< 0.05
	Acute	91%	85%	< 0.01
	Delayed	74%	67%	< 0.05
FLIE total score	Overall	74%	64%	< 0.01

\*NS: not statistically significant

Study 801 compared an aprepitant regimen (n = 244) with a control regimen (n = 245) that included ondansetron given for four days.<sup>21</sup> The study had 96% power to detect a 20% difference in overall CR rates, based on a two sided test at a significance level  $\alpha = 0.05$ , with a sample size of 175 evaluable patients per treatment group. The baseline characteristics of the randomised study groups were well matched with respect to demographics, type of malignancy and chemotherapeutic regimens.

In the modified ITT analysis, significantly more patients in the aprepitant group achieved a CR compared to the control regimen in the overall phase (absolute difference 11.4%, NNT = 9). The aprepitant containing regimen was also significantly more effective than the control regimen in the acute phase (absolute difference 8.4%, NNT = 12) and the delayed phase (absolute difference 11%, NNT = 10). The percentage of patients in the aprepitant group with no emesis was significantly higher than the control group, in all three phases. However, there was no significant difference in the number of patients needing rescue therapy, or for the endpoint of no significant nausea. The results for primary and secondary endpoints for all phases are shown below in Tables 5 and 6.

**Table 5. results of primary endpoints in study 801.<sup>21</sup>**

Primary endpoint	Phase	Aprepitant (n = 243)	Control (n = 241)	p-value
Complete response	Overall	72.0%	60.6%	0.003
	Acute	87.7%	79.3%	0.005
	Delayed	74.1%	63.1%	0.004

**Table 6. results of secondary efficacy endpoints in study 801.<sup>21</sup>**

Primary endpoint	Phase	Aprepitant (n = 243)	Control (n = 241)	p-value
No emesis	Overall	76.5%	62.2%	≤0.001
	Acute	88.9%	80.5%	0.004
	Delayed	79.0%	64.3%	≤0.001
No rescue therapy	Overall	82.3%	79.9%	NS*
	Acute	94.2%	92.9%	NS
	Delayed	83.5%	81.7%	NS
No significant nausea	Overall	73.1%	69.7%	NS
	Acute	92.1%	89.5%	NS
	Delayed	75.9%	72.1%	NS

\*NS: not statistically significant

The effect of aprepitant in multiple cycles of HEC was assessed in an optional multiple cycle extension to studies 052 and 052.<sup>23</sup> Patients who completed the first cycle of these two studies received the same blinded study regimen to which they were originally assigned for a maximum of five further chemotherapy cycles. The analysis used a combined endpoint of full response (FR, defined as no emesis and no significant nausea). In the pooled analyses 61% of patients in the aprepitant group and 46% of patients in the control group achieved a FR in the first-cycle. Thereafter, FR rates for the aprepitant group were 59% by cycle six, and 40% by cycle-six for the control group. Overall the probability of a FR was significantly higher in the aprepitant group than the standard regimen over all six-cycles ( $p \leq 0.006$ ). However, it should be noted that a study specifically designed to show sustained activity over a number of cycles of therapy would need to be re-randomised after the first-cycle of treatment in order to protect the study from potential carry over effects.

### **MODERATELY EMETOGENIC CHEMOTHERAPY (MEC)**

One multi-centre, randomised, double-blind, parallel group study has evaluated the efficacy and safety of aprepitant for the prevention of CINV in patients with breast cancer treated with MEC that included cyclophosphamide with or without doxorubicin or epirubicin (study 071).<sup>24,25</sup> Aprepitant (n = 438) was examined as add-on therapy to ondansetron and dexamethasone on the day of chemotherapy and compared to ondansetron on day two and three post-chemotherapy (n = 428). The dexamethasone dose in the aprepitant group was lower than that in the control group to ensure similar dexamethasone plasma exposure in the two groups (table 7).<sup>24</sup>

**Table 7. Medication regimens in study 071.**<sup>24,25</sup>

Study	Day one		Days two to three		Day four	
	APR	Standard regimen	APR	Standard regimen	APR	Standard regimen
071	APR 125mg Ond 8mg BD Dex 12mg	Ond 8mg BD Dex 20mg	APR 80mg	Ond 8mg BD	-----	-----

APR=aprepitant (oral), Dex=dexamethasone (oral), and Ond=ondansetron (oral).

The primary end point was the proportion of patients achieving a CR (defined as no vomiting and no rescue therapy in the 120 hours after the first cycle of MEC). Patients completed a diary which included the date and time of any emetic episode, the use of rescue medication and daily nausea ratings using a visual analogue scale. The secondary endpoint was the proportion of patients with CINV which had minimal or no effect on daily life as assessed by the FLIE questionnaire. The study had 80% power to detect superiority of the aprepitant regimen if the true effect of this regimen is 10% higher than that of the control regimen, based on a sample size of 375 assessable patients per treatment group. As with the HEC studies, a modified ITT approach was used for all efficacy analyses. Of the 438 and 428 patients randomised to aprepitant and control therapy, 433 and 424, respectively, were included in the efficacy analyses. The reasons for the exclusions were no efficacy data for four patients in each group and one patient in the aprepitant group did not receive chemotherapy.<sup>24</sup>

The baseline characteristics of the randomised study groups were well matched with respect to demographics, type of malignancy, prior and concomitant medications, and chemotherapeutic regimens.<sup>24</sup> With respect to the primary end point, the aprepitant containing regimen was significantly more effective than the standard regimen, with 8.3% more patients achieving a CR in the overall phase, which equates to an NNT of 13 (table 8).<sup>24,25</sup> In the acute phase significantly more patients in the aprepitant group than the control group achieved a CR (absolute difference 7%, NNT = 15). In the delayed phase, however, the difference between the two groups did not reach significance. The number of patients reporting minimal or no impact of CINV on their daily lives was significantly higher in the aprepitant group compared to the control group (63.5% vs. 55.6%;  $p=0.019$ ).<sup>24</sup> Significantly more patients in the aprepitant group than the control group had no emesis in the overall phase (75.7% vs. 58.7%;  $p<0.001$ ), but there were no significant differences between the two groups with respect to use of rescue therapy, overall nausea or significant nausea.<sup>24,25</sup>

**Table 8. complete response rates in modified ITT group in study 071.**<sup>24,25</sup>

Phase	Aprepitant (n = 433)	Standard regimen (n = 424)	p-value
<b>Overall</b>	50.8%	42.5%	0.015
<b>Acute (0 - 24h)</b>	75.7%	69.0%	0.034
<b>Delayed (24 - 120h)</b>	55.4%	49.1%	NS*

\*NS: not statistically significant

The effect of aprepitant in multiple cycles of MEC was assessed in an optional multiple cycle extension of study 071, in which the patients received the same antiemetic regimen they took in the first cycle for up to a further three cycles.<sup>26</sup> Of the 866 patients who were randomised to treatment during the first cycle, 744 (86%) entered the extension phase and 650 (75% of those randomised) completed all four cycles.<sup>26</sup> The number of patients who had a CR in cycle one and sustained a CR over cycles two to four was significantly higher in the aprepitant group compared to those receiving the standard regimen ( $p=0.017$ ). The proportions of patients with no emesis were higher in the aprepitant than the control group for all four cycles ( $p<0.001$ ). However, when the no nausea and no significant nausea components of the CR were considered, there were no significant differences between the two groups during any of the four cycles, with the exception of no significant nausea in cycle two ( $p=0.020$ ). Although the efficacy of aprepitant seemed to be retained over multiple cycles, the data obtained in cycle's two to four do not allow for definitive conclusions regarding the relative efficacy of the two regimens. In a study specifically designed to show sustained activity over a number of cycles of therapy, rather than patients receiving the same study regimen they received for the first cycle, re randomisation after the first-cycle of treatment to prevent a carry over effect would have been a more appropriate study design. The results obtained in cycles 2-4 were omitted from the summary of product characteristics.

## ADVERSE EFFECTS

As expected in a population receiving chemotherapy, most patients receiving treatment experienced an adverse event during clinical trials and therefore the adverse profile of aprepitant is heavily influenced by the cytotoxic treatment.

### HIGHLY EMETOGENIC CHEMOTHERAPY

In the pooled analyses of studies 052 and 054 in patients receiving HEC, adverse reactions considered to be drug related were reported in approximately 17% patients who received the aprepitant regimen compared with 13% who received standard therapy,<sup>22</sup> with serious drug-related adverse reactions occurred in 2% and 4%, respectively.<sup>9</sup> The proportion of patients who discontinued treatment due to drug-related adverse reactions was 3% and 2%, respectively.<sup>9</sup> There was no significant difference in the rate of drug-related laboratory adverse events in the treatment groups (4% vs. 3%, respectively).

In study 801, the treatment groups were similar with respect to the incidence of adverse reactions considered to be drug related (24% vs. 24% for aprepitant and standard therapy, respectively).<sup>21</sup> Serious drug-related adverse reactions occurred in 0.8% and 0.4%, respectively. The proportion of patients who discontinued treatment due to adverse events was 0% and 1.6%, respectively. The rate of drug-related laboratory adverse events was significantly higher in the aprepitant group compared to standard therapy (6% vs. 2%,  $p=0.023$ ).<sup>21</sup>

The most common reported adverse events with higher incidences in the aprepitant containing regimen than the standard regimen reported in patients receiving HEC are summarised in the table 9.

**Table 9. Summary of adverse events in patients receiving HEC.**

<b>Pooled analysis of studies 052 and 054.</b> <sup>9,22</sup>		
<b>Adverse reaction</b>	<b>Aprepitant regimen (n = 544)</b>	<b>Standard regimen (n = 550)</b>
Asthenia/fatigue	18%	12%
Nausea	13%	12%
Hiccups	11%	6%
Anorexia	10%	9%
Diarrhoea	10%	7%
Dizziness	7%	4%
<b>Study 801.</b> <sup>21</sup>		
<b>Adverse reaction</b>	<b>Aprepitant regimen (n = 243)</b>	<b>Standard regimen (n = 244)</b>
Nausea	16%	10%
Dyspepsia	14%	11%
Diarrhoea	13%	9%
Fatigue	9%	6%

### **MODERATELY EMETOGENIC CHEMOTHERAPY**

In patients receiving MEC, the treatment groups were similar with respect to the incidence of adverse reactions considered to be drug related (22% vs. 20%), serious adverse events (3% vs. 4%), and adverse events leading to drug discontinuation (1.6% vs. 1.2%, for aprepitant and standard therapy, respectively).<sup>24,25</sup> Among the most commonly reported drug-related adverse events (incidence >2%), only fatigue was reported more frequently in the aprepitant-containing regimen than in the standard regimen (2.5% vs. 1.6%, respectively).<sup>25</sup>

### **MULTIPLE CYCLES OF CHEMOTHERAPY**

During the multiple cycle chemotherapy extension studies the incidence and pattern of drug-related adverse events were similar across both treatment groups and comparable to those seen in cycle one in each study.<sup>23,26</sup>

### **DOSAGE, ADMINISTRATION AND COST**

Aprepitant is administered orally at a dose of 125 mg once daily on day one and 80 mg once daily on days two and three.<sup>18</sup> An intravenous infusion of fosaprepitant 115 mg over 15 minutes may be substituted for oral aprepitant 125 mg on day one only. Aprepitant is taken as part of an antiemetic regimen that includes a corticosteroid and a 5-HT<sub>3</sub> antagonist.<sup>18</sup> The dosing regimens and the prices of the

regimens and their components, used in the pivotal clinical trials which aprepitant was licensed for HEC and MEC are shown below in Tables 10 and 11, respectively. Prices: eMIMS<sup>27</sup> and electronic Drug Tariff:<sup>28</sup> However, it should be noted that the dexamethasone and ondansetron doses used in these studies are rarely used in UK practice (table 1.), and therefore actual total costs will differ appreciably depending upon local variations in the dose and duration of 5-HT<sub>3</sub> and steroid cover.

**Table 10. Costs of aprepitant containing regimens for HEC**

Drug	Day 1	Day 2	Day 3	Day 4	Total Cost
Aprepitant	125 mg (oral)	80 mg (oral)	80 mg (oral)	None	£47.42
Dexamethasone	12 mg (oral)	8 mg (oral)	8 mg (oral)	8 mg (oral)	£1.57*
Ondansetron	32 mg iv	None	None	None	£47.96†
Whole regimen with oral aprepitant					£96.95

\* Price based on pack size of 500 dexamethasone 2 mg tablets at £43.63.

† Price based on pack size of 5 ondansetron 4ml (2mg per ml) ampoules at £59.95.

**Table 11. Costs of aprepitant containing regimens for MEC**

Drug	Day 1	Day 2	Day 3	Total Cost
Aprepitant	125 mg (oral)	80 mg (oral)	80 mg (oral)	£47.42
Dexamethasone	12 mg (oral)	None	None	£0.52*
Ondansetron	2 x 8 mg (oral)	None	None	£11.85‡
Whole regimen with oral aprepitant				£59.79

\* Price based on pack size of 500 dexamethasone 2 mg tablets at £43.63.

‡ Price based on pack size of 10 ondansetron 8 mg tablets at £59.27.

## PLACE IN THERAPY

In patients receiving HEC, the addition of aprepitant to an antiemetic regimen of ondansetron plus dexamethasone resulted in statistically significant improvements in complete response during the acute, delayed and overall phase compared to ondansetron and dexamethasone alone.<sup>9,21,22</sup> All three studies reported a significant reduction in favour of aprepitant in the number of patients with emesis, but aprepitant

did not consistently reduce nausea. In patients with breast cancer receiving MEC, the number of patients with a complete response was statistically significantly higher in the aprepitant group in the acute and overall phases, but not in the delayed phase.<sup>24,25</sup> Patients receiving aprepitant experienced fewer episodes of emesis overall, but there was no difference in the number of patients who experienced no nausea overall.

There were some limitations with these studies that restrict their applicability to clinical practice. Most notably, in each study aprepitant was compared to a dosage regimen of dexamethasone and ondansetron which are rarely used in the UK due to the potential for increased adverse effects. Significantly higher oral doses were generally used, and ondansetron was given by intravenous infusion in the HEC studies. In the study of MEC, the appropriateness of a comparator regimen where no steroid was used is questionable. Although this may be effective in some patients, standard practice is to combine a corticosteroid with another agent (metoclopramide or a 5-HT<sub>3</sub> antagonist). It is unclear as to whether the primary endpoint would have been reached had the comparison been made to these combinations. Efficacy results in multiple cycles should be interpreted with caution due to the fact that patients may have chosen whether or not to continue into the next cycle based on their response in the previous cycle, therefore leading to a more favourable outcome in later cycles.<sup>24,25</sup>

Studies using more relevant comparators regimens reflecting those commonly used in UK practice are needed to establish the exact place of aprepitant in therapy. However, it is expected that aprepitant will be reserved for use in combination with a 5-HT<sub>3</sub> antagonist and dexamethasone for the prevention of acute and delayed nausea and vomiting due to HEC in patients considered to be at high risk (e.g. poor performance status, and concomitant drug treatments), and in those who have experienced emesis despite treatment with a combination of an 5-HT<sub>3</sub> antagonist and dexamethasone in a previous cycle of HEC. Currently the most expensive drugs for CINV are the 5-HT<sub>3</sub> antagonists. The addition of aprepitant to this regimen will more than double the cost for antiemetic therapy, although this may be partially offset by some reduction in the need for rescue therapy. Aprepitant has not been shown to be cost effective in patients receiving MEC.<sup>17</sup>

Aprepitant is not licensed as a monotherapy and should not replace a 5-HT<sub>3</sub> antagonist in an antiemetic regimen. There are no data supporting the use of aprepitant for the prevention of CINV caused by other less emetogenic chemotherapy regimens, or with radiation induced nausea and vomiting. The use of aprepitant for established nausea and vomiting or for rescue therapy has not been studied.

## ARRANGEMENTS FOR PRESCRIBING

Aprepitant is suitable only for prescribing prior to MEC and HEC in specialist cancer centres or cancer units. It is not envisaged that shared care is appropriate or necessary for this drug.

## FUTURE DEVELOPMENTS

Aprepitant is currently being investigated as part of other antiemetic regimens including palonosetron in the prevention of CINV caused by HEC.<sup>29</sup> Aprepitant is under investigation for the prevention of CINV caused by low emetogenic chemotherapy regimens and radiotherapy.<sup>30</sup> The effect of aprepitant on cyclophosphamide pharmacokinetics in patients with breast cancer is also being studied.<sup>31</sup>

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**APPENDICES**  
**APPENDIX 1.**

**TABLE 12. EMETOGENIC POTENTIAL OF SOME ANTINEOPLASTIC AGENTS**

<b>Emetic Risk</b>	<b>Agent</b>	
<b>High</b> (> 90% frequency of emesis)	Doxorubicin or epirubicin with cyclophosphamide Altretamine Carmustine > 250 mg/m <sup>2</sup> Cisplatin ≥ 50 mg/m <sup>2</sup>	Cyclophosphamide >1,500 mg/m <sup>2</sup> Dacarbazine Mechlorethamine Procarbazine (oral) Streptozocin
<b>Moderate</b> (30 - 90% frequency of emesis)	Aldesleukin >12-15 million units/m <sup>2</sup> Amifostine > 300mg/m <sup>2</sup> Arsenic trioxide Azacitidine Bendamustine Busulfan > 4 mg/day Carboplatin Carmustine ≤ 250 mg/m <sup>2</sup> Cisplatin < 50 mg/m <sup>2</sup> Cyclophosphamide ≤ 1,500 mg/m <sup>2</sup> Cyclophosphamide (oral) Cytarabine > 1 g/m <sup>2</sup> Dactinomycin Daunorubicin	Doxorubicin Epirubicin Etoposide (oral) Idarubicin Ifosfamide Imatinib (oral) Irinotecan Lomustine Melphalan > 50 mg/m <sup>2</sup> Methotrexate 250 to > 1,000 mg/m <sup>2</sup> Oxaliplatin > 75 mg/m <sup>2</sup> Temozolomide (oral) Vinorelbine (oral)
<b>Low</b> (10 - 30% frequency of emesis)	Amifostine ≤ 300mg Bexarotene Capecitabine Cytarabine (low dose) 100 – 200mg/m <sup>2</sup> Docetaxel Doxorubicin (liposomal) Etoposide Fludarabine (oral) 5-Fluorouracil Gemcitabine	Ixabepilone Methotrexate > 50 mg/m <sup>2</sup> to < 250 mg/m <sup>2</sup> Mitomycin Mitoxantrone Nilotinib Paclitaxel Paclitaxel - albumin Pemetrexed Topotecan Vorinostat
<b>Minimal</b> (<10% frequency of emesis)	Alemtuzumab Alpha Interferon Asparaginase Bevacizumab Bleomycin Bortezomib Busulfan Cetuximab Chlorambucil (oral) Cladribine (2-Chloro-deoxyadenosine) Dasatinib Decitabine Denileukin diftitox Dexrazoxane Erlotinib Fludarabine Gefitinib Gemtuzumab ozogamicin	Hydroxyurea (oral) Lapatinib Lenalidomide Melphalan (oral low-dose) Methotrexate ≤ 50 mg/m <sup>2</sup> Nelrabine Panitumumab Pentostatin Rituximab Sorafenib Sunitinib Temsilolimus Thalidomide Thioguanine (oral) Trastuzumab Valrubicin Vinblastine Vincristine Vinorelbine
Adapted from the NCCN Clinical Practice Guidelines in Oncology – Antiemesis. <sup>6</sup>		

**APPENDIX 2. SUMMARY TABLES OF KEY STUDIES**

Key: AE - adverse events; ALT - alanine aminotransferase; AST - aspartate aminotransferase; bd - twice daily; CINV - chemotherapy induced nausea and vomiting; CNS - central nervous system; CR - complete response; DB - double blind; FR - full response; HCG - human chorionic gonadotropin; IV - intravenous; MEC - moderately emetogenic chemotherapy; NR - not reported; NS - not significant; od - once daily; MC - multicentre; RCT - randomised controlled trial; SAE - serious adverse event; ULN - upper limit of normal; vs. - versus; WBC - white blood cell.

Reference	Design	Intervention	Inclusion criteria	Exclusion criteria	Main outcomes	Results (cycle 1 only)	Adverse effects
Hesketh et al, 2003. <sup>19</sup>  EMA 2004 <sup>9</sup>  (STUDY 052)	Phase III, DB, MC, RCT	<p><b>Aprepitant</b> (n = 264)</p> <p>Oral aprepitant 125mg + IV ondansetron 32mg + oral dexamethasone 12mg on day 1.</p> <p>Then oral aprepitant 80mg od on days 2-3 + oral dexamethasone 8mg od on days 2-4</p> <p><b>Standard therapy</b> (n = 266)</p> <p>IV ondansetron 32mg + oral dexamethasone 20mg on day 1.</p> <p>Then oral dexamethasone 8mg bd on days 2-4</p>	<p>Cisplatin naïve patients, &gt;18 years old with histologically confirmed solid tumours, Karnofsky score ≥ 60 and were scheduled to receive their first cycle of chemotherapy including cisplatin ≥ 70 mg/m<sup>2</sup>.</p> <p>Females of child-bearing age required to have negative β-HCG test result.</p>	<p>Current use of illicit drugs/signs of alcohol abuse, abnormal laboratory values (including: WBC &lt;3,000/mm<sup>3</sup>, neutrophil count &lt;1,500/mm<sup>3</sup>, platelet count &lt;100,000/mm<sup>3</sup>, AST &gt;2.5x ULN, ALT &gt;2.5x ULN, bilirubin 1.5x ULN or creatinine &gt;1.5x ULN), multiple-ay cisplatin-based chemotherapy in a single cycle or radiotherapy to abdomen/pelvis within 1 week before study day 1 or between days 1 to 6.</p>	<p><b>Primary endpoint:</b> CR (defined as no emetic episodes and no rescue therapy) in overall phase (days 1 to 5).</p> <p><b>Secondary endpoints:</b> CR in the acute phase (0 to 24 h after cisplatin), CR in the delayed phase (days 2 to 5), no emesis, no significant nausea, complete protection/total control, and impact of CINV on daily life.</p>	<p>Aprepitant (n = 260) vs. standard therapy (n = 261)</p> <p>Primary endpoint: CR in overall phase = 72.7% vs. 52.3% of, p&lt;0.001), respectively.</p> <p>Secondary endpoints: CR in acute phase = 89.2% vs.78.1% (p&lt;0.001), CR in delayed phase = 75.4% vs. 55.8% (p&lt;0.001), no emesis (overall phase) = 77.7% vs. 55% (p&lt;0.05), complete protection (overall phase) = 63.4% vs. 49.2% (p&lt;0.05), CINV minimal or no impact on daily life = 74.0% vs. 64.3% (p=NR), respectively.</p> <p>Total control, and no significant nausea, in the overall phase (difference = NS)</p>	<p>Aprepitant (n = 261) vs. standard therapy (n = 264)</p> <p>The overall incidence of AEs was similar between the aprepitant and standard therapy groups (65% vs. 61%), with SAEs occurring in 16% vs. 17%, respectively. AEs deemed to be drug related occurred in 15% vs. 11%, of patients respectively.</p> <p>The most common AEs with higher incidences in the aprepitant group than the standard therapy group were; asthenia/fatigue 17% vs. 10%; hiccups 14% vs. 7% and nausea 11% vs. 9%</p>

Reference	Design	Intervention	Inclusion criteria	Exclusion criteria	Main outcomes	Results (cycle 1 only)	Adverse effects
Poli Bigelli et al, 2003. <sup>20</sup> EMEA 2004. <sup>9</sup>  (STUDY 054)	As study 052	As study 052  <b>Aprepitant</b> (n = 283)  <b>Standard therapy</b> (N = 286)	As study 052	As study 052	<b>Primary endpoint</b> As study 052  <b>Secondary endpoints</b> As study 052	Aprepitant (n = 260) vs. standard therapy (n = 263)  <b>Primary endpoint:</b> CR in overall phase = 62.7% vs. 43.3% of, p<0.001, respectively.  <b>Secondary endpoints:</b> CR in acute phase = 82.8% vs. 68.4% (p<0.001), CR in delayed phase = 67.7% vs. 46.8% (p<0.001), no emesis (overall phase) = 66% vs. 44% (p<0.01), complete protection (overall phase) = 56% vs. 41% (p<0.01), total control (overall phase) = 44% vs. 32% (p<0.01), CINV minimal or no impact on daily life = 74.7% vs. 63.5% (p=NR), respectively.  No significant nausea in the overall phase (difference p=NS)	Aprepitant (n = 282) vs. standard therapy (n = 285)  The overall incidence of AEs was similar between the aprepitant and standard therapy groups (73% vs. (73%), with SAEs occurring in 11% vs. 10%, respectively. AEs deemed to be drug related occurred in 20% vs. 14%, of patients respectively.  The most common AEs with higher incidences in the aprepitant group than the standard therapy group were; asthenia/ fatigue 18% vs. 14%; anorexia 15% vs. 14% and diarrhoea 12% vs. 11%

Reference	Design	Intervention	Inclusion criteria	Exclusion criteria	Main outcomes	Results (cycle 1 only)	Adverse effects
<p>Warr, Grunberg et al, 2005.<sup>22</sup></p> <p>EMA 2004.<sup>9</sup></p> <p><b>(052 &amp; 054 pooled)</b></p>	<p>Pre-planned pooled analyses of data from studies 052<sup>19</sup> and 054<sup>20</sup></p>	<p>As studies 052 and 054</p> <p>Pooled analyses;</p> <p><b>Aprepitant</b> (n = 520)</p> <p><b>Standard</b> therapy (n = 523)</p>	<p>As studies 052 and 054</p>	<p>As studies 052 and 054</p>	<p>Pooled analyses of studies 052 and 054</p> <p><b>Primary endpoint:</b> CR (defined as no emetic episodes and no rescue therapy) in overall phase (days 1 to 5).</p> <p><b>Secondary endpoints:</b> CR in the acute phase (0 to 24 h) after cisplatin), CR in the delayed phase (days 2 to 5), no emesis, no significant nausea, complete protection, and impact of CINV on daily life.</p>	<p>Aprepitant (n = 520) vs. standard therapy (n = 523)</p> <p><b>Primary endpoint:</b> CR in overall phase = 68% vs. 48% of, p&lt;0.001, respectively.</p> <p><b>Secondary endpoints:</b> CR in acute phase = 86% vs. 73% (p&lt;0.001), CR in delayed phase = 72% vs. 51% (p&lt;0.001), no emesis (overall phase) = 72% vs. 50% (p&lt;0.01), complete protection (overall phase) = 60% vs. 45% (p&lt;0.01), no nausea (overall phase) 48% vs. 42% (p&lt;0.05), No significant nausea (overall phase) 72% vs. 65% (p&lt;0.05), CINV minimal or no impact on daily life = 74% vs. 64% (p&lt;0.01), respectively.</p>	<p>Consistent with those of individual studies 502 and 504</p> <p>Aprepitant (n = 544) vs. standard therapy (n = 550)</p> <p>The overall incidence of AEs was similar between the aprepitant and standard therapy groups (69% vs. (67%), with SAEs occurring in 13% vs. 14%, respectively. AEs deemed to be drug related occurred in 17% vs. 13%, of patients respectively.</p> <p>The most common AEs with higher incidences in the aprepitant group than the standard therapy group were; asthenia/ fatigue 18% vs. 12%; nausea 13% vs. 12%; hiccups 11% vs. 6%; diarrhoea 10% vs. 7%, and anorexia 10% vs. 9%</p>

Reference	Design	Intervention	Inclusion criteria	Exclusion criteria	Main outcomes	Results (cycle 1 only)	Adverse effects
Schmoll et al, 2006. <sup>21</sup>  (STUDY 801)	Phase III, DB, MC, RCT	<p><b>Aprepitant</b> (n = 244)</p> <p>Oral aprepitant 125mg + IV ondansetron 32mg + oral dexamethasone 12mg on day 1.</p> <p>Then oral aprepitant 80mg od on days 2-3 + oral dexamethasone 8mg od on days 2-4</p> <p><b>Control regimen</b> (n = 245)</p> <p>IV ondansetron 32mg + oral dexamethasone 20mg on day 1.</p> <p>Then oral ondansetron 8mg bd + oral dexamethasone 8mg bd on days 2-4.</p>	Cisplatin naïve patients, >18 years old with confirmed solid tumours, scheduled to receive their first cycle of chemotherapy including cisplatin $\geq 70 \text{ mg/m}^2$ , Karnofsky score $\geq 60$ , life expectancy $\geq 3$ months. Females of child-bearing age required to have negative $\beta$ -HCG test result.	Concomitant stem cell rescue therapy, planned multiple day cisplatin based chemotherapy in cycle 1, MEC within 6 days before or after cisplatin, receipt of 5-HT <sub>3</sub> receptor antagonist within 48hrs of day 1, radiotherapy to abdomen/pelvis within 1 week before day 1 to day 6, active infection, primary or symptomatic CNS malignancy, emesis 24hrs before cisplatin, and abnormal laboratory values (including: WBC $< 3,000/\text{mm}^3$ , neutrophil count $< 1,500/\text{mm}^3$ , platelet count $< 100,000/\text{mm}^3$ , AST $> 2.5 \times \text{ULN}$ , ALT $> 2.5 \times \text{ULN}$ , bilirubin $> 1.5 \times \text{ULN}$ or creatinine $> 1.5 \times \text{ULN}$ ).	<p><b>Primary endpoint:</b> CR (defined as no emetic episodes and no rescue therapy) in overall phase (days 1 to 5).</p> <p><b>Secondary endpoints:</b> CR in the delayed phase (days 2 to 5), and no emesis.</p> <p>Other endpoints reported include: CR in the acute phase (0 to 24 h), no significant nausea and rescue therapy</p>	<p>Aprepitant (n = 243) and standard therapy (n = 241)</p> <p><b>Primary endpoint:</b> CR in overall phase = 72% vs. 61% (p=0.003), respectively.</p> <p><b>Secondary endpoints:</b> CR in delayed phase = 74% vs. 63% (p=0.004), no emesis (overall phase) = 77% vs. 63% (p&lt;0.001).</p> <p>CR in acute phase = 88% vs. 79% (p=0.005), no significant nausea and no rescue therapy (difference in all phases p=NS)</p>	<p>Aprepitant (n = 243) and standard therapy (n = 244)</p> <p>The overall incidence of AEs was similar between the aprepitant and standard therapy groups (79% vs. (82%), with SAEs occurring in 14% vs. 15%, respectively. AEs deemed to be drug related occurred in 24% vs. 24%, of patients respectively.</p> <p>The most common AEs with higher incidences in the aprepitant group than the standard therapy group were; nausea 16% vs. 10%; dyspepsia 14% vs. 11%; diarrhoea 13% vs. 9% and fatigue 9% vs. 6%.</p>

Reference	Design	Intervention	Inclusion criteria	Exclusion criteria	Main outcomes	Results (cycle 1 only)	Adverse effects
<p>Warr, Hesketh et al, 2005.<sup>24</sup></p> <p>EMA 2008.<sup>25</sup></p> <p><b>(STUDY 071)</b></p>	Phase III, DB, MC, RCT	<p>Aprepitant (n = 438)</p> <p>Oral aprepitant 125mg + oral ondansetron 8mg bd + oral dexamethasone 12mg on day 1.</p> <p>Then oral aprepitant 80mg od on days 2-3</p> <p>Control regimen (n = 428)</p> <p>Oral ondansetron 8mg bd + oral dexamethasone 20mg on day 1.</p> <p>Then oral ondansetron 8mg bd on days 2-3</p>	MEC naïve patients, ≥18 years old with breast cancer, scheduled to receive their first cycle of MEC (cyclophosphamide, doxorubicin, epirubicin, ether alone or in combination), Karnofsky score ≥60, and a life expectancy of ≥4 months.	Symptomatic CNS malignancy, received abdominal/pelvic radiation therapy in week before treatment, vomited in 24hrs before treatment day 1, active infection, systemic fungal infection, or any severe concurrent illness, abnormal laboratory values (including: WBC <3,000/mm <sup>3</sup> , neutrophil count <1,500/mm <sup>3</sup> , platelets count <100,000/mm <sup>3</sup> , AST >2.5x ULN, ALT >2.5x ULN, bilirubin 1.5x ULN or creatinine >1.5x ULN), systemic corticosteroid therapy, no antiemetics (except single daily doses of lorazepam).	<p>Primary endpoint: CR (defined as no emetic episodes and no rescue therapy) in overall phase (days 1 to 5).</p> <p>Secondary endpoints: Impact of CINV on daily life.</p> <p>Other endpoints reported include: CR in the delayed (days 2 to 5) and acute phase (0 to 24 h), no emesis, no rescue therapy, and no significant nausea.</p>	<p>Aprepitant (n = 433) vs. control (n = 424)</p> <p>Primary endpoint: CR in overall phase = 51% vs. 42% of, p=0.015), respectively.</p> <p>Secondary endpoints: CINV minimal or no impact on daily life = 64% vs. 56% (p=0.19), respectively.</p> <p>CR in acute phase = 76% vs.69% (p=0.034), no emesis (overall phase) = 76% vs. 59% (p&lt;0.01).</p> <p>CR in delayed phase, and no rescue therapy in all phases (p=NS)</p>	<p>Aprepitant (n = 438) vs. control (n = 428)</p> <p>The overall incidence of AEs was similar between the aprepitant and standard therapy groups (73% vs. (75%), with SAEs occurring in 3% vs. 4%, respectively. AEs deemed to be drug related occurred in 22% vs. 20%, of patients respectively.</p> <p>The most common AEs with higher incidences in the aprepitant group than the standard therapy group were; alopecia 24% vs. 22%; dyspepsia 8% vs. 5%, stomatitis 5% vs. 4%, hot flush 3% vs. 1%, and pharyngo-laryngeal pain 3% vs. 2%.</p>

Reference	Design	Intervention	Inclusion criteria	Exclusion criteria	Main outcomes	Results (cycle 1 only)	Adverse effects
De Wit et al, 2004. <sup>23</sup> <b>(052 &amp; 054 extension)</b>	Multiple-cycle extension of studies	Same regimen to which originally assigned in studies 052 and 054, for up to five additional cycles	As studies 052 and 054	As studies 052 and 054	FR (defined as no emesis and no significant nausea (days 1-5 after each cycle))	In every cycle FR was significantly higher in the aprepitant group ( $p < 0.006$ ) compared to the control group.  FR in the first cycle was 61% (n = 516) group vs. 46% (n = 522), and 59% (n = 89) vs. 40% (n = 78) by cycle six, respectively.  (n = number included in efficacy analysis)	The incidence and pattern of drug-related adverse events were similar across both treatment groups and comparable to those seen in cycle one in each study
Herrstedt et al, 2005. <sup>26</sup> <b>(071 extension)</b>	Multiple-cycle extension of study 071	Same regimen to which originally assigned in study 071, for up to five additional cycles	As study 071	As study 071	CR (defined as no emesis and no rescue therapy) in cycles 2-4 and sustained CR across multiple cycles.	In every cycle CR was significantly higher in the aprepitant group ( $p < 0.017$ ) compared to the control group.  CR in the first cycle was 51% (n = 433) group vs. 43% (n = 424), and 35% (n = 141) vs. 24% (n = 95) by cycle four, respectively.  (n = number included in efficacy analysis)	The incidence and pattern of drug-related adverse events were similar across both treatment groups and comparable to those seen in cycle one in each study