Drugs 2009; 69 (13): 1853-1878
0012-6667/09/0013-1853/$55.55/0

© 2009 Adis Data Information BV. All rights reserved.

# Aprepitant

## A Review of its Use in the Prevention of Nausea and Vomiting

*Monique P. Curran* and *Dean M. Robinson*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Philadelphia, Pennsylvania, USA

**Various sections of the manuscript reviewed by:**
***P. De Negri***, Department of Anesthesia, Intensive Care and Pain Medicine, IRCCS Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, Potenza, Italy; ***P. Glare***, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; ***M. Markman***, M.D. Anderson Cancer Center, University of Texas, Houston, Texas, USA; ***H.-J. Schmoll***, Departments of Internal Medicine and Oncology/Hematology, Martin Luther University Halle/Wittenberg, Halle/Saale, Germany; ***S.J.P. Van Belle***, Department of Medical Oncology, University Hospital Ghent, Ghent, Belgium.

**Data Selection**
**Sources:** Medical literature published in any language since 1980 on 'aprepitant', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.
**Search strategy:** MEDLINE, EMBASE and AdisBase search terms were 'aprepitant' and ('chemotherapy-induced nausea and vomiting' or 'CINV') and ('postoperative nausea and vomiting' or 'PONV'). Searches were last updated 27 July 2009.
**Selection:** Studies in patients at risk of developing chemotherapy-induced or postoperative nausea and vomiting who had received aprepitant. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.
**Index terms:** Aprepitant, prevention of chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

## Contents

Summary . . . 1854
1. Introduction . . . 1856
2. Pharmacodynamic Properties . . . 1856
3. Pharmacokinetic Properties . . . 1857
   3.1 Absorption and Distribution . . . 1857
   3.2 Metabolism and Elimination . . . 1857
   3.3 Special Populations . . . 1857
   3.4 Drug Interactions . . . 1858
4. Therapeutic Efficacy . . . 1858
   4.1 Chemotherapy-Induced Nausea and Vomiting (CINV) . . . 1858
      4.1.1 Highly Emetogenic Chemotherapy . . . 1860
      4.1.2 Moderately Emetogenic Chemotherapy . . . 1863
      4.1.3 Special Populations . . . 1865
   4.2 Postoperative Nausea and Vomiting (PONV) . . . 1866
5. Pharmacoeconomic Considerations . . . 1866
6. Tolerability . . . 1868
   6.1 CINV . . . 1868
      6.1.1 Highly Emetogenic Chemotherapy . . . 1868

HELSINN EXHIBIT 2001
Azurity Pharmaceuticals, Inc. v. Helsinn Healthcare S.A.
IPR2025-00947

6.1.2 Moderately Emetogenic Chemotherapy . . . 1869
6.2 PONV . . . 1871
7. Dosage and Administration . . . 1871
8. The Place of Aprepitant in the Prevention of Nausea and Vomiting . . . 1872

## Summary

**Abstract**

Aprepitant (Emend®) is a neurokinin-1 ($NK_1$) receptor antagonist that is able to alleviate the emetic effects of substance P. When combined with a standard regimen of a corticosteroid (dexamethasone) and a serotonin 5-$HT_3$ receptor antagonist (ondansetron), oral aprepitant (125 mg on day 1 then 80 mg once daily on days 2 and 3) was effective in the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with single or multiple cycles of highly emetogenic chemotherapy (HEC). This aprepitant regimen was also effective in the prevention of CINV in patients treated with single or multiple cycles of moderately emetogenic chemotherapy (MEC). A single oral dose of aprepitant 40 mg administered prior to patients undergoing abdominal surgery was also effective in the prevention of postoperative nausea and vomiting (PONV). Aprepitant was generally well tolerated. Aprepitant is a recommended option for the treatment of PONV, and when combined with a corticosteroid and 5-$HT_3$ receptor antagonist is a recommended regimen for the treatment of CINV.

**Pharmacological Properties**

Aprepitant is a selective, high-affinity antagonist at human $NK_1$ receptors and is consequently able to alleviate the emetic effects of substance P. Aprepitant has little or no affinity for serotonin 5-$HT_3$, dopamine or corticosteroid receptors. Aprepitant crosses the blood-brain barrier. Aprepitant had no effect on gastrointestinal motor function in healthy volunteers.

The pharmacokinetics of aprepitant are nonlinear across the recommended dose range, with clearance and absolute bioavailability decreasing with increasing dose. Following administration of a single oral dose of aprepitant 40 mg (recommended dosage in the prevention of PONV) to healthy volunteers, the area under the plasma concentration-time curve (AUC) from time zero to infinity was 7.8 μg • h/mL and the maximum plasma concentration ($C_{max}$) was 0.7 μg/mL. The median time to $C_{max}$ ($t_{max}$) was ≈3.0 hours. Following administration of oral aprepitant 125 mg on day 1 followed by 80 mg once daily on days 2 and 3 (recommended dosage in the prevention of CINV) to healthy volunteers, the AUC from 0 to 24 hours, the $C_{max}$ and $t_{max}$ were 19.6 μg • h/mL, 1.6 μg/mL and ≈4 hours, respectively, on day 1 and 21.2 μg • h/mL, 1.4 μg/mL and ≈4 hours, respectively, on day 3. Aprepitant is excreted largely as metabolites in the urine and via biliary excretion in the faeces. The apparent terminal half-life was 9–13 hours.

Since aprepitant is metabolized by cytochrome P450 (CYP) 3A4, coadministration of aprepitant and inhibitors or inducers of this isoenzyme will induce changes in the plasma levels of aprepitant. As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered substances that are metabolized through CYP3A4. As a moderate inducer of CYP2C9 and a mild inducer of CYP3A4, aprepitant can decrease plasma concentrations of substrates metabolized by these isoenzymes.

**Therapeutic Efficacy**

In phase III studies in patients with solid tumours treated with a single cycle of HEC, an aprepitant regimen (containing aprepitant 125 mg on day 1 then 80 mg once daily on days 2 and 3 plus dexamethasone and ondansetron) resulted in significantly higher complete response (no emesis and no rescue therapy) rates than with the

© 2009 Adis Data Information BV. All rights reserved. 

control regimen of ondansetron plus dexamethasone (63–73% vs 43–61%; $p < 0.01$) during the overall (day 1–5) phase after HEC administration. Complete response rates during the acute phase (day 1; 83–89% vs 68–79%) and the delayed phase (days 2–5; 68–75% vs 47–63%) were also significantly higher with the aprepitant than with the control regimen. In particular, the rate of no emesis was significantly higher with the aprepitant than the control regimen during the acute, delayed and overall phases. In a multiple-cycle extension study in which patients received of up to five additional cycles of HEC, the efficacy of the aprepitant regimen was maintained throughout each of the multiple cycles.

In patients with breast cancer treated with MEC (cyclophosphamide ± anthracycline), an aprepitant regimen (aprepitant plus dexamethasone plus ondansetron), compared with a control regimen (dexamethasone plus ondansetron) resulted in more patients achieving a complete response during the overall phase (51% vs 42%; $p = 0.015$), according to data from a large phase III trial. The between-group difference in complete response rates was primarily driven by the rate of no emesis (76% vs 59%; unadjusted p-value $< 0.001$), with no significant between-group difference for the use of rescue medication. In a multiple-cycle extension of this trial, the advantage of the antiemetic effect of the aprepitant regimen over the control regimen seen in the first cycle was maintained throughout the additional three cycles of MEC. In a large phase III trial in patients with a variety of malignancies receiving MEC, significantly more recipients of a single cycle of an aprepitant than a control regimen had no emesis (76% vs 62%; $p < 0.001$) and a complete response (69% vs 56%; $p < 0.001$) during the overall phase.

An aprepitant regimen compared with a control regimen was considered to be cost-effective with regard to the cost per QALY in the prevention of CINV in two European studies, although not according to a US analysis.

Although a large phase III trial failed to prove that a single dose of oral aprepitant 40 mg was superior to ondansetron in preventing PONV (as measured by the proportion of patients with complete response in the 24 hours after surgery), a second phase III trial of similar design established that a single dose of aprepitant 40 mg was noninferior to ondansetron, with 64% versus 55% of patients achieving a complete response. Aprepitant was significantly more effective than ondansetron at preventing vomiting in the 24 and 48 hours after surgery in both studies ($p < 0.001$).

## Tolerability

An antiemetic regimen containing dexamethasone, ondansetron and aprepitant (administered administered orally as a single 125 mg dose on day 1 and then 80 mg once daily on days 2 and 3) was generally well tolerated when used in the prevention of CINV in cancer patients receiving single or multiple cycles of HEC or MEC. The incidence of adverse events in recipients of an aprepitant regimen was similar to that in recipients of the control regimen (dexamethasone plus ondansetron). Commonly reported adverse events (≥10% of recipients) were asthenia/fatigue, nausea, hiccups, constipation, diarrhoea and anorexia. Laboratory adverse events (≥3% of recipients) included proteinuria and increases in ALT, AST, blood urea nitrogen and serum creatinine. The adverse event profile of an aprepitant regimen in patients receiving MEC was generally similar to that reported in patients receiving HEC.

The tolerability profile of a single oral dose of aprepitant 40 mg when used in the prevention of PONV was similar to that of a single intravenous dose of ondansetron in patients undergoing open, abdominal surgery who participated in two, large, well controlled studies. Most adverse events were mild to moderate in intensity. Commonly reported adverse events (≥5% of recipients of either treatment group) were constipation, nausea, pruritus, pyrexia, hypotension, headache and flatulence.

© 2009 Adis Data Information BV. All rights reserved.

## 1. Introduction

Nausea and vomiting are common adverse events experienced by patients following chemotherapy or surgery.[1-4] Poorly controlled chemotherapy-induced nausea and vomiting (CINV) or postoperative nausea and vomiting (PONV) can lead to dehydration, malnutrition and electrolyte imbalance, and may be associated with a variety of complications including oesophageal tears, declining behavioural and mental status, and wound dehiscence. These symptoms can result in a reduced willingness of the patient to be treated in the future or delays in discharge from hospital.

PONV can occur in as many as 79% of patients,[3] while approximately 70–80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting, with 10–40% of cancer patients experiencing anticipatory nausea and/or vomiting.[4] The incidence and severity of CINV are affected by a number of factors including the chemotherapy involved, the dosage of the chemotherapy, the schedule and route of administration of the chemotherapy and patient-related factors such as age, sex and history of alcohol use.[4]

Nausea and/or vomiting induced by chemotherapy are commonly classified as acute, delayed, anticipatory, breakthrough and refractory (table I).

Vomiting results from the stimulation of a multistep reflex pathway controlled in the brain.[2] Vomiting is triggered when afferent impulses travel from the chemoreceptive trigger zone, the pharynx, the gastrointestinal (GI) tract and the cerebral cortex to the vomiting centre in the brain (located in the medulla). Efferent impulses then travel from the vomiting centre to the salivation centre, abdominal muscles, respiratory centre and cranial nerves causing vomiting.

**Table I.** Types of chemotherapy-induced nausea and/or vomiting

| | |
|---|---|
| Acute | Occurs within a few minutes to several hours after chemotherapy and usually resolves within 24 hours |
| Delayed | Occurs more than 24 hours after chemotherapy |
| Anticipatory | Occurs before a cycle of chemotherapy. A conditioned response |
| Breakthrough | Occurs despite prophylactic treatment and/or requires rescue antiemetic agents |
| Refractory | Occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles |

Agents that have been used in the prevention of vomiting are those that block neurotransmitter receptors in the CNS and GI tract that mediate the afferent inputs, and include serotonin 5-$HT_3$ receptor antagonists, corticosteroids, dopamine receptor antagonists and neurokinin-1 ($NK_1$) receptor antagonists. Since no single agent can be expected to provide complete protection against the various phases of emesis, a combination of antiemetic agents are usually administered.

Aprepitant (Emend®) is a selective, high-affinity $NK_1$ receptor antagonist that blocks the binding of substance P.[5] This review examines the pharmacological properties, therapeutic efficacy, pharmacoeconomics and tolerability of orally administered aprepitant in the prevention of PONV in surgical patients, and in the prevention of CINV in cancer patients treated with highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC).

## 2. Pharmacodynamic Properties

The pharmacodynamic properties of aprepitant have been reviewed previously;[5] therefore, only a brief summary is provided herein.

Aprepitant selectively, and with high affinity, blocks the binding of substance P at $NK_1$ receptors in the CNS;[6] *in vitro*, the aprepitant concentration that displaced 50% of substance P from the $NK_1$ receptors was 0.12 nmol/L.[7]

Aprepitant had low affinity for $NK_2$ and $NK_3$ receptors. It had little or no affinity for the serotonin 5-$HT_3$, dopamine or corticosteroid receptors (other neurotransmitters involved in the control of emesis).[6]

*In vivo* and human positron emission tomography studies demonstrate that aprepitant crosses the blood-brain barrier and occupies brain $NK_1$ receptors.[7-9] A 125 mg dose of aprepitant resulted in ≥90% occupancy of $NK_1$ receptors in the CNS.[9]

Aprepitant displayed acute- and delayed-phase antiemetic effects in cisplatin-induced emesis in animal models[6,7,10,11] and augments

© 2009 Adis Data Information BV. All rights reserved.

the antiemetic effect of the corticosteroid dexamethasone or the 5-$HT_3$ receptor antagonist ondansetron in animal[11] and human studies (see section 4).

Aprepitant had no effect on GI motor function in healthy volunteers.[12]

## 3. Pharmacokinetic Properties

Data in this section have largely been obtained from the US[6] and European[13] prescribing information.

### 3.1 Absorption and Distribution

Following administration of a single oral dose of aprepitant 40 mg (recommended dosage in the prevention of PONV; see section 7) in the fasted state, the area under the plasma concentration-time curve (AUC) from time zero to infinity was 7.8 μg • h/mL and the maximum plasma concentration ($C_{max}$) was 0.7 μg/mL.[6] The median time to $C_{max}$ was ≈3.0 hours. Administration of a single dose of aprepitant 40 mg with a standard breakfast decreased the aprepitant $C_{max}$ by 18% but did not affect AUC.[13] The decrease in $C_{max}$ was not considered to be clinically relevant.

The pharmacokinetic profile of oral aprepitant administered as a single dose of 125 mg on day 1 followed by 80 mg once daily on days 2 and 3 (recommended dosage for the prevention of CINV; see section 7) to healthy volunteers is shown in table II.[6,13] The mean absolute oral bioavailability of aprepitant decreased with increasing dose; after doses of 80 and 125 mg under fasting conditions was 67% and 59%.[13] Food had no clinically meaningful effect on the bioavailability of aprepitant.[6,13]

**Table II.** Pharmacokinetic parameters of oral aprepitant when administered as a single 125 mg dose on day 1 followed by 80 mg once daily on days 2 and 3.[6,13] Twelve healthy volunteers were enrolled in the open-label study

| Pharmacokinetic parameters | Day 1 | Day 3 |
|---|---|---|
| Mean $C_{max}$ (μg/mL) | 1.6 | 1.4 |
| Mean $AUC_{24}$ (μg • h/mL) | 19.6 | 21.2 |
| Median $t_{max}$ (h) | ≈4 | ≈4 |
| Mean $t_{½β}$ (h) | | ≈9–13 |

**$AUC_{24}$** = area under the concentration-time curve from time 0 to 24 hours; **$C_{max}$** = maximum plasma concentration; **$t_{max}$** = time to $C_{max}$; **$t_{½β}$** = elimination half-life.

Total protein binding of aprepitant is >95% and the mean apparent volume of distribution at steady state is ≈70 L.[6] Aprepitant crosses the blood-brain barrier in humans and the placenta in animal studies.[6]

### 3.2 Metabolism and Elimination

Aprepitant undergoes extensive metabolism.[6,13] Metabolism occurs largely as a result of oxidation at the morpholine ring and its side chain.[14] Seven weakly active metabolites have been identified. *In vitro* studies using human liver microsomes suggested that mainly cytochrome P450 (CYP) 3A4 and to a lesser extent CYP1A2 and CYP2C19 (but not CYP2D6, CYP2C9 or CYP2E1) were involved in the metabolism of aprepitant.[6,15] The unchanged drug accounted for ≈24% of the radioactivity in the plasma following administration of a single oral dose of [$^{14}$C]-aprepitant to healthy volunteers.[6]

Aprepitant is excreted largely as metabolites in the urine and via biliary excretion in the faeces.[6,13] After a single 100 mg intravenous dose of a prodrug of [$^{14}$C]-aprepitant to healthy volunteers, 57% of the radioactivity was detected in the urine and 45% in the faeces. The apparent plasma clearance was dose dependent, decreasing with increasing dose and was ≈62–90 mL/min and the apparent terminal elimination half-life was ≈9–13 hours.[6]

### 3.3 Special Populations

The pharmacokinetic profile of a 3-day regimen of aprepitant (125 mg on day 1 and then 80 mg/day on days 2 and 3) in 17 adolescent cancer patients[16] was similar to that in 12 healthy adult patients (data obtained from a previous study[17]). There are no clinically significant differences in the pharmacokinetics of aprepitant between male and female patients, between races (White, Black and Hispanic), between patients aged ≥65 years and those aged <65 years, and between healthy volunteers and patients with mild to moderate hepatic insufficiency, those with severe renal insufficiency or those requiring

© 2009 Adis Data Information BV. All rights reserved.

haemodialysis.[6,13,18] In these patients, no dosage adjustment is necessary. No data are available regarding the pharmacokinetics in patients with severe hepatic insufficiency.

### 3.4 Drug Interactions

Aprepitant is a substrate and dose-dependent inhibitor of CYP3A4, and an inducer of CYP3A4, CYP2C9 and potentially other isoenzymes.[6,13,15]

Since aprepitant is metabolized by CYP3A4, coadministration of aprepitant and inhibitors or inducers of this isoenzyme will induce changes in the plasma levels of aprepitant (table III).[6,13] Consequently, drugs such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir, which are strong inhibitors of CYP3A4, should be avoided as they may result in increased plasma concentrations of aprepitant. Moderate inhibitors of CYP3A4 (e.g. diltiazem) should be administered with caution. Agents that strongly induce CYP3A4 activity (e.g. rifampicin [rifampin], carbamazepine, phenytoin) may decrease the plasma level of aprepitant and should be avoided.[13]

As a moderate inhibitor of CYP3A4, a 3-day regimen of aprepitant (125 mg on day 1 and then 80 mg/day on days 2 and 3) may increase plasma concentrations of coadministered substances that are metabolized by CYP3A4 (table III). A single dose of aprepitant 40 mg is not expected to increase the plasma concentrations of agents that are metabolized by CYP3A4. Aprepitant should not be used concurrently with pimozide, terfenadine, astemizole or cisapride.[6,13] Docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine and vincristine are agents that are metabolized by CYP3A4. However, there was no significant change in the pharmacokinetic parameters of docetaxel[23] or vinorelbine[24] when these agents were coadministered with a 3-day aprepitant regimen (table III). Nevertheless, careful monitoring is advised when aprepitant is coadministered with any chemotherapeutic agent that is metabolized by CYP3A4. The corticosteroids dexamethasone and methylprednisolone are substrates of CYP3A4 and their plasma levels are increased when coadministered with aprepitant (table III). Therefore, it is recommended that the usual oral dexamethasone dosage should be reduced by approximately 50%, the usual intravenous methylprednisolone dosage should be reduced by approximately 25%, and the usual oral methylprednisolone dosage should be reduced by approximately 50% when coadministered with a 3-day regimen of aprepitant.[6,13]

Because aprepitant has been shown to induce CYP2C9, coadministration of aprepitant with agents that are known to be metabolized by CYP2C9, such as warfarin, tolbutamide and phenytoin, may result in lower plasma concentrations of these agents (table III); therefore, caution is advised.[6,13]

Aprepitant reduced the plasma levels of coadministered oral hormonal contraceptives (table III); therefore, the efficacy of oral contraceptives may be reduced. Alternative or back-up methods of contraception are advised for 1 month following the last dose of aprepitant.[6,13]

## 4. Therapeutic Efficacy

This section focuses on the efficacy of aprepitant when used as part of an antiemetic regimen in the prevention of CINV in adult or adolescent cancer patients (section 4.1) and when used as monotherapy in the prevention of PONV in adult surgical patients (section 4.2). The endpoints used in these trials are shown in table IV.

### 4.1 Chemotherapy-Induced Nausea and Vomiting (CINV)

The efficacy of aprepitant in the prevention of CINV has been evaluated in adult patients receiving HEC (section 4.1.1) or MEC (section 4.1.2) and in adolescent patients receiving emetogenic chemotherapy (section 4.1.3). Focus will be on phase III trials in which aprepitant was administered as part of an antiemetic regimen that also included a corticosteroid (dexamethasone) and a serotonin 5-$HT_3$ receptor antagonist (ondansetron). Aprepitant was administered orally as a single 125 mg dose on day 1 and then 80 mg once daily on days 2 and 3. Specific details of the regimens and the

© 2009 Adis Data Information BV. All rights reserved.

**Table III.** Drug interactions involving aprepitant. Agents were administered orally in healthy volunteers unless otherwise stated

| Agent | Dose of aprepitant (mg) [day(s) administered] | Dosage of concomitant agent (mg[a]) [day(s) administered] | Clinically meaningful pharmacokinetics effects | |
|---|---|---|---|---|
| | | | aprepitant | concomitant agent |
| **Antiemetics** | | | | |
| Dexamethasone (CYP3A4 substrate)[6,13,19] | 125 [1] then 80 [2–5] | 20 [1] then 8 [2–5] | None | ↑ AUC 2.2-fold (day 1 and 5) |
| Granisetron[20] | 125 [1] then 80 [2, 3] | 2 [1] | None | None |
| Methylprednisolone (CYP3A4 substrate)[6,13,19] | 125 [1] then 80 [2, 3] | 125 IV [1] then 40 [2, 3] | None | ↑ AUC 1.34-fold (day 1) and 2.5-fold (day 3) |
| Ondansetron (IV)[20] | 375 [1] then 250 [2–5] | 32 [1] | None | None |
| Palonosetron (IV)[21] | 125 [1] then 80 [2, 3] | 0.25 [1] | None | None |
| **Chemotherapeutic agents** | | | | |
| Cyclophosphamide[22] | 125 [1] then 80 [2, 3] | Recommended regimen | | None |
| Docetaxel[23] | 125 [1] then 80 [2, 3] | Recommended regimen | None | None |
| Vinorelbine[24] | 125 [1] then 80 [2, 3] | Recommended regimen | None | None |
| **CYP3A4 inhibitors** | | | | |
| Diltiazem[6,15] | 230[b] [1–5] | 360 [1–5] | ↑ AUC 2-fold | ↑ AUC 1.7-fold |
| Ketoconazole[6,13,15] | 125 [1] | 400 [1–10] | ↑ AUC ≈5-fold<br>↑ $t_{½}$ 3-fold | None |
| **CYP3A4 inducer** | | | | |
| Rifampicin[6,13] | 375 [9] | 600 [1–14] | ↓ AUC 11-fold<br>↓ $t_{½}$ 3-fold | None |
| **CYP3A4 substrates** | | | | |
| Midazolam[6,13] | 125 [1] then 80 [2–5] | 2 [1 and 5] | None | ↑ AUC 2.3-fold (day 1) and 3.3-fold (day 5) |
| Midazolam (IV)[6,13] | 125 [1] then 80 [2,3] | 2 [0, 4, 8, 15] | None | ↑ AUC 25% (day 4) and ↓19% (day 8) |
| Midazolam[6] | 40 [1] | 2 [1] | None | ↑ AUC 1.2-fold (day 1) |
| **CYP2C9 substrates** | | | | |
| Tolbutamide[6,13] | 125 [1] then 80 [2, 3] | 500 [0, 4, 8, 15] | None | ↓ AUC by 23%, 28% and 15% on days 4, 8 and 15 |
| Warfarin[6,13,17] | 125 [1] then 80 [2, 3] | Titrated to stable INR | None | ↓ $C_{min}$ of S-warfarin by 34% (day 8)<br>↓ INR by 14% (day 5) |
| **CYP2D6 substrate** | | | | |
| Paroxetine[6,13] | 85 or 170[b] | 20 [1–14] | ↓ AUC ≈25%<br>↓ $C_{max}$≈20% | ↓ AUC ≈25%<br>↓ $C_{max}$ ≈20% |
| **Other agents** | | | | |
| Digoxin[25] | 125 [7] then 80 [8–11] | 0.25 [1–13] | None | None |
| Oral contraceptives[6,13] | 100 [1–14] | EE 35 μg [1–21]<br>NOR 1 [1–21] | None | ↓ AUC of EE by 43%<br>↓ AUC of NOR by 8% |
| | 125 [1] then 80 [2, 3] | EE [1–21]<br>NOR [1–21] | | ↓ AUC of EE by 19% (day 10)<br>↓ $C_{min}$ of EE by ≤64% (days 9–21)<br>↓ $C_{min}$ of NOR by ≤60% |

a Unless otherwise stated.

b Administered in tablet form once daily; dosage comparable to capsule formulation stated.

**AUC** = area under the concentration-time curve; **$C_{max}$** = maximum plasma concentration; **$C_{min}$** = trough plasma concentrations; **CYP** = cytochrome P450; **EE** = ethinyl estradiol; **INR** = International Normalized Ratio; **IV** = intravenous; **NOR** = norethisterone (norethindrone); **$t_{½}$** = elimination half-life; ↓ indicates decreases; ↑ indicates increases.

© 2009 Adis Data Information BV. All rights reserved.

**Table IV.** Efficacy endpoints for randomized, double-blind, phase III trials involving aprepitant regimens used in the prevention of nausea and vomiting in patients receiving chemotherapy or post-operatively in patients who have undergone surgery

| Endpoint | Definition |
|---|---|
| No emesis | No vomiting (oral expulsion of stomach contents), retching or dry heaves (an attempt to vomit that is not productive of stomach contents) regardless of use of rescue medication |
| No rescue therapy | No use of medication to treat established nausea or emesis |
| No nausea | Maximum nausea VAS rating <5 mm |
| No significant nausea | Maximum nausea VAS rating <25 mm |
| Complete response | No emesis (or no vomiting) and no rescue therapy |
| Complete protection | No emesis (or no vomiting), no rescue therapy, no significant nausea |
| The impact of CINV on daily life | FLIE[26] total score >108 out of a maximum possible score of 126 |

**CINV** = chemotherapy-induced nausea and vomiting; **FLIE** = Functional Living Index Emesis; **VAS** = visual analog scale from 0 ('no nausea') to 100 mm ('worst possible nausea').

dosage of each of the other antiemetic agents involved in the trials are presented in table V (HEC) and table VI (MEC).

The efficacy of an aprepitant-containing regimen was assessed during the acute (0–24 hours), delayed (25–120 hours) and overall (0–120 hours) phases after the administration of HEC or MEC. The primary endpoint in these studies was generally the overall complete response rate (table IV). The primary analysis generally involved the modified intent-to-treat (mITT) population (patients who received chemotherapy, at least one dose of the study drug and had at least one post-treatment assessment during cycle 1).

#### *4.1.1 Highly Emetogenic Chemotherapy*

Dose-ranging, phase II studies demonstrated the efficacy of aprepitant when added to a standard antiemetic regimen (corticosteroid plus a 5-$HT_3$ receptor antagonist) in the prevention of CINV during single[33] or multiple[34] cycles of cisplatin-based HEC. The phase II trials supported the use of the corticosteroid dexamethasone for the control of acute emesis and demonstrated the need to lower the dosage of dexamethasone in order to compensate for the inhibition of its metabolism by aprepitant (see section 3.4). Since the first emetic episodes occurred within the first 3 days of cisplatin administration, and given the relatively long half-life of aprepitant (see section 3), aprepitant was administered over 3 days in the subsequent phase III trials.

Three randomized, double-blind, multicentre, phase III trials assessed the efficacy of aprepitant in combination with dexamethasone and ondansetron in the prevention of CINV in adult patients treated with a single cycle of cisplatin-based HEC.[27-29] Two trials (one conducted primarily in the US and EU[27] and the other conducted only in Latin America[28]) were designed to be identical to allow the subsequent pooling and analysis of data.[35-38]

Patients (n = 530,[27] 569[28] and 489[29]) scheduled to receive cisplatin ≥70 mg/m$^2$ were randomized to treatment with either an aprepitant regimen (aprepitant plus dexamethasone plus ondansetron) or a control regimen (dexamethasone plus ondansetron; table V). In two of the trials,[27,28] ondansetron was administered intravenously on day 1 only (table V). In the third phase III trial,[29] ondansetron was administered intravenously on day 1 and then orally on days 2–4 (table V).

Patients (n = 851) who had completed a single cycle of HEC from the two identical phase III trials[27,28] continued in a multiple-cycle, double-blind, extension study in which patients were treated with up to an additional five cycles of HEC.[36]

Additional antiemetic agents were not permitted within 2 days prior to cisplatin adminis-

**Table V.** Aprepitant (APR) or control (CON) regimens used in phase III trials in patients treated with highly emetogenic chemotherapy

| Regimen | Dose (mg) [day(s) administered] |
|---|---|
| APR[27-29] | APR 125 [1] PO[a] then 80 od [2, 3] PO |
| | DEX 12 [1] PO[b] then 8 od [2–4] PO |
| | OND 32 [1] IV |
| CON[27,28] | DEX 20 [1] PO[b] then 8 bid [2–4] PO |
| | OND 32 [1] IV |
| CON[29] | DEX 20 [1] PO[b] then 8 bid [2–4] PO |
| | OND 32 [1] IV then 8 bid [2–4] PO |

a Administered 1 h prior to chemotherapy.

b Administered 30 min prior to chemotherapy.

**bid** = twice daily; **DEX** = dexamethasone; **IV** = intravenously; **od** = once daily; **OND** = ondansetron; **PO** = orally.

© 2009 Adis Data Information BV. All rights reserved.

**Table VI.** Aprepitant (APR) or control (CON) regimens used in phase III trials in patients treated with moderately emetogenic chemotherapy. All agents were administered orally

| Regimen | Dose (mg) [day(s) administered] |
|---|---|
| APR[30-32] | APR 125 [1][a] then 80 od [2, 3]<br>DEX 12 [1][b]<br>OND 8 bid [1] |
| CON[30-32] | DEX 20 [1][b]<br>OND 8 bid [1–3] |

a Administered 1 h prior to chemotherapy.

b Administered 30 minutes prior to chemotherapy.

**bid** = twice daily; **DEX** = dexamethasone; **od** = once daily; **OND** = ondansetron.

tration (day 1) or between days 1–6 (except as rescue medication for established nausea or vomiting). Additional HEC (Hesketh level ≥3) was permitted only on day 1 and was administered to 10–17% of patients.[27-29] Concomitant therapy administered in addition to cisplatin included etoposide, fluorouracil, gemcitabine, vinorelbine, paclitaxel, cyclophosphamide, doxorubicin and docetaxel.[6]

Patients included in the studies were cisplatin-naive, aged ≥18 years, with solid tumours confirmed by histology, a Karnofsky score ≥60 and a life expectancy greater ≥3 months. Exclusion criteria included abnormal laboratory values (for platelets, absolute neutrophils, AST, ALT, bilirubin or creatinine), a planned multiple-day, cisplatin-based chemotherapy regimen in a single cycle, MEC or HEC in the 6 days prior to and/or after the day of cisplatin administration, radiation therapy to the abdomen or pelvis within 1 week before HEC administration or on days 1–6 after HEC.[27-29]

### Single-Cycle Chemotherapy

Phase III studies in patients with solid tumours treated with a single cycle of HEC demonstrated that a regimen containing aprepitant plus dexamethasone plus ondansetron resulted in significantly more patients with an overall complete response (primary endpoint) than with the control regimen of dexamethasone plus ondansetron alone (63–73% vs 43–61%; $p < 0.01$ for all comparisons; table VII).[27-29] Complete response rates during the acute (83–89% vs 68–79%) and delayed (68–75% vs 47–63%) phases were also significantly higher with the aprepitant than with the control regimen (see table VII for p-values).

A combined analysis[38] of the two identical phase III trials[27,28] indicated that the aprepitant regimen provided greater overall complete response than the control regimen irrespective of sex (women 66% vs 41%, $p < 0.001$; men 69% vs 53%, $p < 0.001$).

Significantly more patients treated with the aprepitant than the control regimen had no emesis during the acute, delayed and overall phases (table VII), according to data from all three trials.[27-29] Moreover, Kaplan-Meier analysis indicated that the time to the first emesis after the initiation of HEC was longer with the aprepitant regimen than the control regimen ($p < 0.001$; based on the log-rank test).[27-29] Combined data from the two identical studies indicated the difference between the two groups on the Kaplan-Meier curves began at approximately 12–16 hours after HEC administration (statistical analyses not reported).[39] Similarly, in the third study,[29] the Kaplan-Meier curves for each of the treatment regimens began to visually separate at 10 hours, with the between-group difference being significant after 21 hours ($p < 0.05$; backwards log-rank procedure).

According to a combined analysis[35] of the two identical phase III trials,[27,28] delayed emesis was correlated with, but not entirely dependent upon, the presence of acute emesis. Across both studies, acute emesis occurred in 13% of recipients of the aprepitant regimen and 26% of recipients of the control regimen ($p < 0.01$). Of these patients, the incidence of subsequent delayed emesis was 17% lower with the aprepitant compared with the control regimen. Of the patients who did not experience acute emesis, the incidence of delayed emesis was 16% less with aprepitant than with the control. Thus, it was concluded by the researchers that aprepitant conferred a similar degree of improvement in delayed phase protection, irrespective of acute emesis. They concluded that the decrease in delayed emesis could not be attributed to a 'carry over' effect that resulted from a decrease in acute emesis.

The effect of aprepitant on nausea was not as apparent as its effect on emesis. In one study,[28] there was a significant difference between the

© 2009 Adis Data Information BV. All rights reserved.

**Table VII.** Clinical efficacy of an oral aprepitant (APR) antiemetic regimen in patients (pts) receiving one cycle of highly emetogenic cisplatin-based chemotherapy[a] in randomized, double-blind, multicentre, phase III trials.[27-29] Data have also been obtained from the aprepitant manufacturer's US prescribing information[6] and the EU summary of product characteristics.[13] Pts were randomized to an APR (APR plus dexamethasone plus ondansetron) or a control (CON) regimen (dexamethasone plus ondansetron; see table V for further dosage and administration details). Placebo tablets/capsules were administered to maintain blinding. Endpoints were assessed during the acute (day 1), delayed (days 2–5) or overall (days 1–5) phases after chemotherapy. Analyses were performed on the modified intent-to-treat population[b]

| Study | Regimen (pt no.) | Phase | Endpoint[c] (% pts) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | complete response | complete protection | no emesis | no nausea | no significant nausea | no rescue medication |
| Hesketh et al.[27] | APR | Acute | 89*** | 85** | 90** | 72[d] | 91[d] | 94* |
| | (260) | Delayed | 75*** | 66** | 81** | 51 | 75 | 81* |
| | | Overall | 73***[e] | 63** | 78** | 48 | 73 | 81** |
| | CON | Acute | 78 | 75 | 79 | 69[d] | 87[d] | 89 |
| | (261) | Delayed | 56 | 52 | 59 | 48 | 69 | 74 |
| | | Overall | 52[e] | 49 | 55 | 44 | 66 | 71 |
| Poli-Bigelli et al.[28] | APR | Acute | 83*** | 80** | 84** | | | 96** |
| | (261)[f] | Delayed | 68*** | 61** | 72** | 53** | 73 | 83* |
| | | Overall | 63***[e] | 56** | 66** | 49* | 71 | 82** |
| | CON | Acute | 68 | 65 | 69 | | | 90 |
| | (263) | Delayed | 47 | 44 | 48 | 40 | 65 | 74 |
| | | Overall | 43[e] | 41[e] | 44 | 39 | 64 | 73 |
| Schmoll et al.[29] | APR | Acute | 88** | | 89** | | 92 | 94 |
| | (243) | Delayed | 74** | | 79*** | | 76 | 84 |
| | | Overall | 72**[e] | | 77**[e] | | 73 | 82 |
| | CON | Acute | 79 | | 81 | | 90 | 93 |
| | (241) | Delayed | 63 | | 64 | | 72 | 82 |
| | | Overall | 61[e] | | 62[e] | | 70 | 80 |

a Pts received a single dose of intravenous cisplatin ≥70 mg/m$^2$ on day 1 of cycle 1.

b Pts who received chemotherapy and at least one dose of the study drug and had at least one post-treatment assessment during cycle 1.

c See table IV for definition of endpoints.

d Statistical analysis not performed.

e Primary endpoint.

f There were 261 pts in the acute phase and 260 pts in the delayed and overall phases.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs CON.

aprepitant and control regimen in the number of patients with no nausea in the delayed and overall phases (table VII). There was no between-group difference in the number of patients with no significant nausea in any of the three studies.[27-29]

The number of patients requiring rescue medication was significantly lower in recipients of the aprepitant regimen than the control regimen during all phases after chemotherapy in two[27,28] of the three[27-29] trials (table VII).

Two studies assessed the impact of CINV on daily life, according to the total score on the Functional Living Index Emesis (FLIE) questionnaire (see table IV for further explanation of this endpoint).[27,28] Significantly more recipients of the aprepitant than the control regimen experienced minimal or no impact of CINV on daily living, according to data from the two individual studies (75% vs 64%[28] and 74% vs 64%;[27] statistical analyses not reported) or from a combined analysis of the two studies (74% vs 64%; $p < 0.01$; analysis not adjusted for multiplicity).[35]

### Multiple-Cycle Chemotherapy

In patients who continued into the multiple-cycle extension study,[36] the efficacy of the aprepitant regimen was maintained throughout each of the multiple HEC cycles (up to five additional

© 2009 Adis Data Information BV. All rights reserved.

cycles; see figure 1). In every cycle, the estimated probability of no emesis and no significant nausea over the 5 days after HEC administration was significantly higher with the aprepitant than the control regimen (see figure 1).

#### 4.1.2 Moderately Emetogenic Chemotherapy

Randomized, double-blind, multicentre, phase III trials assessed the efficacy of aprepitant in combination with dexamethasone and ondansetron in the prevention of CINV in adult patients with breast cancer[30] or various malignancies[31] who were treated with a single cycle of MEC.

Patients (n = 866[30] and 848[31]) were randomized to treatment with an aprepitant (aprepitant plus dexamethasone plus ondansetron) regimen or a control (dexamethasone plus ondansetron) regimen (see table VI for further details). In addition, patients (n = 744) who had completed one cycle of MEC from one of these trials[30] entered a double-blind, multiple-extension study during which they received up to three additional cycles of MEC.[40] A smaller, double-blind, single-centre study also randomized 127 Chinese patients receiving MEC to an aprepitant or control regimen (table VI).[32] All agents were administered orally.

Eligible patients were aged ≥18 years of age, naive to MEC or HEC, had histologically confirmed breast cancer[30,32] or any histologically or cytologically confirmed malignant disease[31] requiring treatment with non-cisplatin-based MEC, Karnofsky scores ≥60 and a predicted life expectancy of ≥4 months. Exclusion criteria included a symptomatic, CNS malignancy, vomiting in the 24 hours prior to treatment, abnormal laboratory values (platelets, absolute neutrophils, AST, ALT, bilirubin or creatinine), planned cisplatin-based chemotherapy, MEC or HEC in the week prior to treatment, radiation therapy to the abdomen or pelvis within 1 week of treatment and up to 6 days after treatment, or systemic corticosteroid use.

In the studies in patients with breast cancer,[30,32] patients were scheduled for treatment with intravenous cyclophosphamide 750–1500 mg/m$^2$ monotherapy, or intravenous cyclophosphamide 500–1500 mg/m$^2$ plus intravenous doxorubicin ≤60 mg/m$^2$ or epirubicin ≤100 mg/m$^2$.

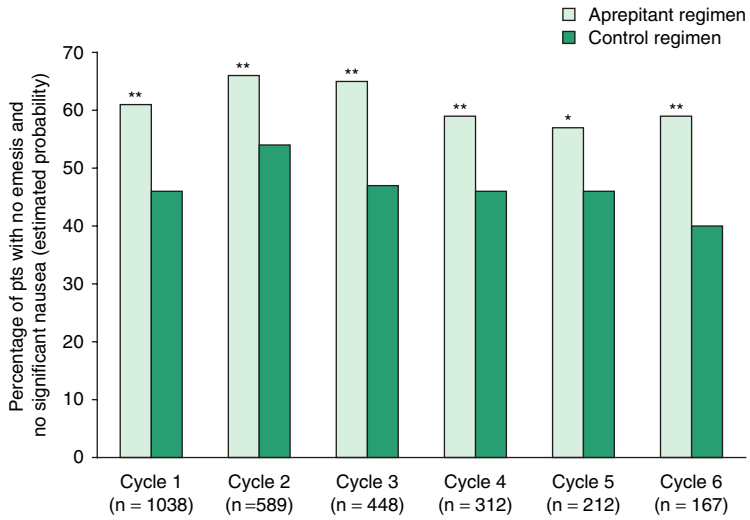


**Fig. 1.** Estimated probability of overall rate of cancer patients (pts) with no emesis and no significant nausea after treatment with an aprepitant (aprepitant plus dexamethasone plus ondansetron) or control (dexamethasone plus ondansetron) regimen in the 5 days after administration of highly emetogenic, cisplatin-based chemotherapy (HEC). Pooled data[36] from the multiple-cycle extensions of two randomized, double-blind, multicentre studies.[27,28] Pts received an aprepitant or control regimen (see table V for details of dosage) for up to an additional five cycles of HEC. Analyses are based on the modified intent-to-treat population and used a transitional probabilities approach. * $p < 0.01$, ** $p < 0.001$ vs control.

© 2009 Adis Data Information BV. All rights reserved.

**Table VIII.** Clinical efficacy of oral aprepitant (APR) in the prevention of chemotherapy-induced nausea and vomiting in patients (pts) with breast cancer[30] or various malignancies[31] receiving moderately emetogenic chemotherapy. Data were obtained from the modified intent-to-treat population[a] of randomized, double-blind, multicentre,[30,31] phase III trials. Data have also been obtained from the US prescribing information[6] and the EU summary of product characteristics.[13] Pts were randomised to an APR regimen (APR plus dexamethasone plus ondansetron) or a control (CON) regimen (dexamethasone plus ondansetron; see table VI for further details of dosage and days of administration). All antiemetic agents were administered orally. Placebo tablets/capsules were administered to maintain blinding. Efficacy endpoints were assessed in cycle 1 during the acute (day 1), delayed (days 2–5) or overall (days 1–5) phase after administration of chemotherapy

| Study | Regimen (pt no.) | Phase | Endpoint[b] (% of pts) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | complete response | complete protection | no emesis | no nausea | no significant nausea | no rescue medication |
| Rapoport et al.[31] | APR | Acute | 89** | | 92** | | | |
| | (425) | Delayed | 71** | | 78** | | | |
| | | Overall | 69** | | 76**[c] | | | |
| | CON | Acute | 80 | | 84 | | | |
| | (407) | Delayed | 61 | | 67 | | | |
| | | Overall | 56 | | 62[c] | | | |
| Warr et al.[30] | APR | Acute | 76* | | 88** | | 80 | 83 |
| | (433) | Delayed | 55 | | 81** | | 65 | 63 |
| | | Overall | 51*[c] | 43 | 76** | 33 | 61 | 59 |
| | CON | Acute | 69 | | 77 | | 78 | 80 |
| | (424) | Delayed | 49 | | 69 | | 62 | 60 |
| | | Overall | 42[c] | 37 | 59 | 33 | 56 | 56 |

a Pts who received chemotherapy and at least one dose of the study drug and had at least one post-treatment assessment during cycle 1.

b See table IV for definition of endpoints.

c Primary endpoint.

* $p < 0.05$, ** $p < 0.001$ vs CON (values not adjusted for multiplicity).

In the other study, patients with various malignancies were scheduled to be treated with a single dose of one or more of the following chemotherapeutic agents: any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, or doxorubicin; intravenous cyclophosphamide <1500 mg/m$^2$; or intravenous cytarabine >1 g/m$^2$.[31] The various types of malignancies included breast (52% of patients), colorectal (20%), lung (13%) and ovarian cancer (4.6%).

### Single-Cycle Chemotherapy

In patients with breast cancer treated with MEC, an aprepitant regimen, compared with a control regimen, was significantly more effective for the prevention of CINV, according to data from the large phase III trial.[30] Significantly ($p < 0.05$) more patients treated with the aprepitant regimen had an overall complete response (primary endpoint) than with the control regimen alone (table VIII). Complete responses during the acute phase (table VIII) were also significantly higher with the aprepitant regimen than with the control regimen. When the separate components of complete response were analysed, significantly (unadjusted p-value < 0.001) more recipients of the aprepitant than the control regimen reported no emesis during the overall, acute and delayed phases, but there was no significant difference between the groups for the use of rescue medication for any phase (table VIII). There was no significant difference between the groups during the overall phase for the percentage of patients reporting no nausea or no significant nausea.

Assessment of the impact of vomiting and nausea on the patients' daily lives (using the FLIE questionnaire) indicated that a higher proportion of patients treated with the aprepitant than the control regimen reported no or minimal impact on daily living overall (64% vs 56%; $p = 0.019$), with significant differences favouring aprepitant in the vomiting domain score (86% vs

© 2009 Adis Data Information BV. All rights reserved.

72%; p < 0.001), but not the nausea domain score (54% vs 51%).[30]

Significantly (p < 0.001) more recipients of an aprepitant than a control regimen had no emesis (primary endpoint) and a complete response during the overall phase, according to preliminary data from a large phase III trial in patients with a variety of malignancies receiving MEC (table VIII). Significantly more recipients of the aprepitant regimen than the control regimen had no emesis and a complete response during the acute and delayed phases (table VIII).[31]

In a smaller, single-centre trial in Chinese patients with breast cancer treated with MEC, there was no significant difference between the treatment groups for the number of patients who reported complete responses, complete protection, no vomiting, no significant nausea, no nausea or no rescue medication during the overall, acute or delayed phases.[32] However, the impact of vomiting and nausea on the patients' daily lives (assessed according to the FLIE questionnaire) for the vomiting domain was significantly less for those treated with aprepitant than those treated with the control regimen (mean score 3.40 vs 23.99; p = 0.0002), although there was no significant between-group difference for the total score or for the nausea domain.[32]

#### Multiple-Cycle Chemotherapy

In a multiple-cycle extension[40] of the large phase III trial in patients with breast cancer,[30] the advantage of the antiemetic effect of the aprepitant regimen over the control regimen seen in cycle 1 (complete response 51% vs 43%; p = 0.015) was maintained throughout the additional three cycles of MEC (figure 2).

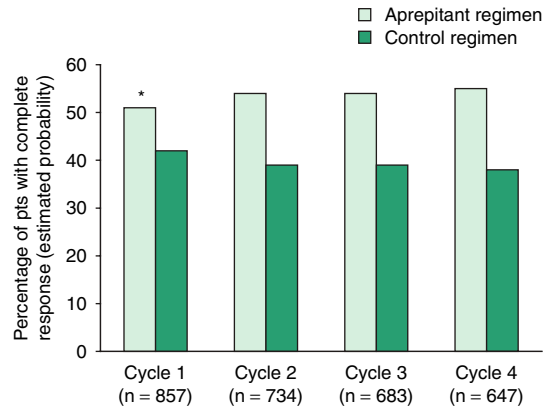


**Fig. 2.** Estimated probability of complete response in an individual cycle in the 5 days after treatment with moderately emetogenic chemotherapy (MEC) in breast cancer patients (pts).[40] Pts (n = 744) who had completed one cycle of chemotherapy in a randomized, double-blind, multicentre study (866 pts initially randomized) entered the multiple-cycle, extension study during which they received an additional three cycles of MEC and an aprepitant (aprepitant plus dexamethasone plus ondansetron) or control regimen (dexamethasone plus ondansetron; see table VI for details of dosage and days of administration) to prevent nausea and emesis. Analyses are based on the modified intent-to-treat population and used a transitional probabilities approach. * p = 0.015; statistical analyses not reported for cycles 2–4.

#### 4.1.3 Special Populations

A randomized, double-blind, multicentre trial compared the efficacy of an aprepitant regimen (aprepitant plus dexamethasone plus ondansetron) with a control regimen (dexamethasone plus ondansetron) in the prevention of CINV in adolescent patients (n = 46) scheduled for treatment with emetogenic chemotherapy or a previously intolerable chemotherapy due to CINV.[16] Four patients also received open-label treatment with the aprepitant regimen.

Specific details of each regimen and the dosage of each of the antiemetic agents involved are presented in table IX. Patients were aged 11–19 years with confirmed malignancy and a Karnofsky score ≥60. Most patients had bone sarcoma (53% treated with the aprepitant regimen and 83% treated with the control regimen).[16]

Rates of complete response in the overall, acute and delayed phase were 29%, 61% and 36% in recipients of the aprepitant regimen and 6%, 39% and 6% with the control regimen, with no statistically significant difference between the two treatment groups.[16] Rates of no emesis and no use of rescue medication (during the acute, delayed and overall phase), and overall rates of no nausea were not significantly different between the two treatment groups. However, the study was not sufficiently powered to demonstrate a between-group difference in efficacy and the lack of statistical significance may have been due to the small sample size.

© 2009 Adis Data Information BV. All rights reserved.

**Table IX.** Aprepitant (APR) or control (CON) regimens used in a randomized, double-blind multicentre trial in adolescent patients aged 11–19 years treated with emetogenic chemotherapy. APR and DEX were administered orally and OND was administered intravenously

| Regimen | Dose [day(s) administered] |
|---|---|
| APR | APR 125 mg [1][a] then 80 mg od [2, 3] |
| | DEX 8 mg [1][b] then 4 mg od [2–4] |
| | OND 0.45 mg/kg [1] |
| CON | DEX 16 mg [1][b] then 8 mg od [2–4] |
| | OND 0.45 mg/kg [1] |

a Administered 1 h prior to chemotherapy.

b Administered 30 minutes prior to chemotherapy.

**DEX** = dexamethasone; **od** = once daily; **OND** = ondansetron.

### 4.2 Postoperative Nausea and Vomiting (PONV)

The efficacy of aprepitant was compared with that of ondansetron for the prevention of PONV in randomized, double-blind, multicentre, phase III trials in patients undergoing open, abdominal surgery under general anaesthesia.[41,42] This section focuses on data pertaining to the approved 40 mg dose of aprepitant.

Patients (n = 922[41] and 805[42]) were randomized to receive a single dose of oral aprepitant 40 or 125 mg (administered with 50 mL of water 1–3 hours before anaesthesia), or an intravenous dose of ondansetron 4 mg (administered immediately before induction of anaesthesia). Patients could not receive additional prophylactic antiemetics within 24 hours pre-operatively, intra-operatively or postoperatively, although patients could receive rescue antiemetics for established PONV.

Patients were aged ≥18 years with an American Society of Anesthesiologists physical status class of I–III and were scheduled to undergo open abdominal surgery requiring an overnight stay in hospital and to receive volatile agent-based anaesthesia including nitrous oxide. Patients who had vomited within the previous 24 hours or due to an organic aetiology were excluded from the trials.[41,42]

Of the 564 patients who received aprepitant 40 mg in both these trials,[41,42] 92% were women (who were mainly undergoing gynaecological surgery), 58% were White, 13% Hispanic American, 7% multi-racial, 14% Black, 6% Asian and 2% were from other races.[6] The mean age of patients treated with aprepitant 40 mg was 46.1 years (range 19–84 years).[6]

A primary efficacy endpoint in both trials was the complete response rate (see table IV for definition) in the 24 hours after surgery in the mITT population (866[41] and 733[42] patients). A co-primary endpoint in one of the trials was the rate of no vomiting in the 24 hours after surgery.[41] One trial assessed the noninferiority of aprepitant compared with ondansetron;[41] noninferiority was achieved if the lower bound for the one-sided 95% CI for the odds ratio of aprepitant versus ondansetron was >0.65.

One of the studies failed to met the primary hypothesis that aprepitant was superior to ondansetron, as measured by the proportion of patients with complete response.[42] However, the second study established that a single dose of aprepitant 40 mg was noninferior to ondansetron in achieving complete response (odds ratio 1.4; lower bound of the one-sided 95% CI was 1.04).[41]

Aprepitant 40 mg was significantly more effective than ondansetron at preventing vomiting at 24 and 48 hours after surgery in both studies ($p < 0.001$; table X).[41,42] Moreover, during the first 48 hours after surgery, aprepitant 40 mg, compared with ondansetron, delayed the time to the first vomiting episode ($p < 0.001$) in both studies. More aprepitant 40 mg than ondansetron recipients had no significant nausea ($p < 0.05$; table X) in one of the studies.[41] There was no significant between-group difference in the number of patients who did not require rescue medication (table X) in either of the studies.

According to *post hoc* analyses of pooled data from both of these trials, aprepitant 40 mg was significantly more effective than ondansetron for each of the five endpoints (figure 3) in the 24 hours after surgery, including: no significant nausea; no nausea; no vomiting; no nausea and no vomiting; and no nausea, no vomiting and no use of rescue medication.[43]

## 5. Pharmacoeconomic Considerations

A number of analyses have examined the cost effectiveness of an aprepitant regimen relative to

© 2009 Adis Data Information BV. All rights reserved.

**Table X.** Clinical efficacy of oral aprepitant (APR) compared with that of ondansetron (OND) in the prevention of postoperative nausea and vomiting in surgical patients (pts) in two, randomized, double-blind, multicentre, phase III trials.[41,42] Pts received a single oral dose of APR 40 or 125 mg (administered with 50 mL of water 1–3 hours before anaesthesia), or an intravenous dose of OND 4 mg (administered immediately before induction of anaesthesia)

| Study | Dose (mg) | No. of pts (mITT) | Complete response[a] (% of pts) 0–24 h[b] | No vomiting (% of pts) | | No rescue medication (% of pts) 0–24 h | No significant nausea[c] (% of pts) 0–24 h |
|---|---|---|---|---|---|---|---|
| | | | | 0–24 h | 0–48 h | | |
| Diemunsch et al.[41] | APR 40 | 293 | 64[d] | 84** | 82** | 67 | 62* |
| | APR 125 | 293 | 63 | 86** | 85** | 65 | 60 |
| | OND 4 | 280 | 55 | 71 | 66 | 63 | 53 |
| Gan et al.[42] | APR 40 | 248 | 45 | 90** | 85**[e] | 45 | 50 |
| | APR 125 | 239 | 43 | 95** | 90**[f] | 44 | 49 |
| | OND 4 | 246 | 42 | 74 | 67[e] | 46 | 43 |

a Defined as no vomiting and no use of rescue medication.

b Primary endpoint.

c Peak verbal rating scores of 0–4 on an 11-point scale; 0 (no nausea) to 10 (nausea as bad as could be).

d Noninferior to OND (lower bound of one-sided 95% CI >0.65).

e Data obtained from the US prescribing information.[6]

f Estimated from a graph.

**mITT** = modified intent-to-treat population; * $p < 0.05$, ** $p < 0.001$ vs OND.

a control regimen for the prevention of CINV in patients treated with HEC or MEC from a healthcare payer perspective.[44-46] Dosages of the agents involved in the regimens from the studies involved are presented in table V (HEC) and table VI (MEC). Further details of the methodology of the pharmacoeconomic studies are shown in table XI.

An aprepitant regimen compared with a control regimen was considered to be cost effective with regard to the cost per quality-adjusted life-year (QALY) in the prevention of CINV in two European studies,[44,45] although not according to a US analysis.[46] In the Belgian study,[45] an aprepitant regimen was predicted to dominate a control regimen for both MEC and HEC (i.e. were less expensive and more effective) based on incremental costs per QALY gained in both the trial-based and real-life approach that were tested in the model (year of costing 2005). The aprepitant regimen was estimated to be cost effective relative to the control regimen in the prevention of CINV during HEC in the German study, if a threshold value of €43 600 per QALY gained was used (year of costing 2004).[44] However, in the US analysis,[46] the incremental cost per QALY gained for the aprepitant regimen relative to the control regimen administered over five cycles of HEC exceeded the commonly accepted cost-effectiveness threshold of $US50 000 per QALY (year of costing 2005).

In the European studies, analyses demonstrated that the results were most sensitive to changes in the costs of hospitalization, rescue medication (German study[44]) and the cost of ondansetron (Belgian study). In the US study, sensitivity analyses indicated that the aprepitant regimen may be cost effective relative to the control regimen when rescue medication is costly or where the risk of delayed CINV is high.[46]

Pharmacoeconomic analyses, including those of aprepitant regimens, are subject to a number of limitations. Pharmacoeconomic analyses based on clinical trials extrapolate the results of such trials to the general population; however, patient populations, rates of compliance and major outcomes in clinical trials may differ from those observed in real-life practice. Modelled analyses, such as those presented in this section, rely on a number of assumptions and use data from a variety of sources. Results of pharmacoeconomic analyses may not be applicable to other

© 2009 Adis Data Information BV. All rights reserved.

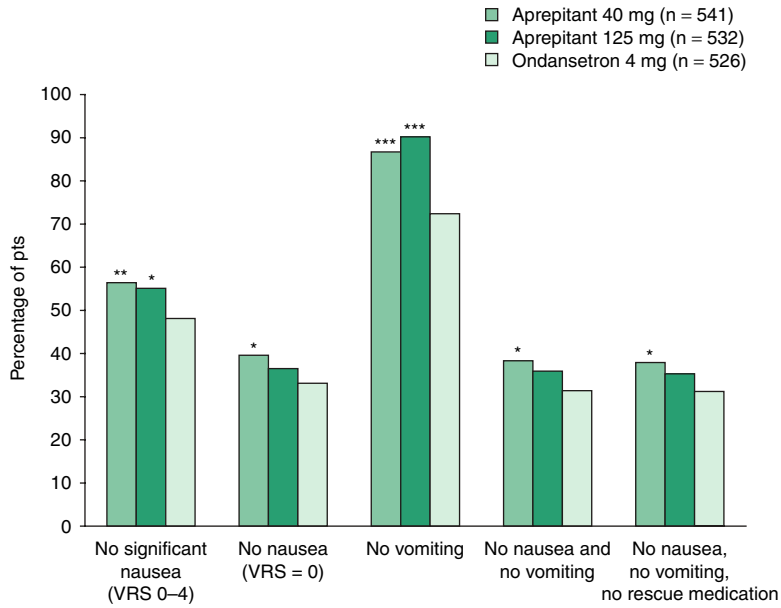


**Fig. 3.** *Post hoc* analysis of efficacy of aprepitant compared with ondansetron in the prevention of nausea and vomiting in the 24 hours after patients (pts) had undergone open abdominal surgery.[43] Combined analysis of data from the modified intent-to-treat population (n = 1559) from two randomized, double-blind trials.[41,42] Pts were randomized to receive a single dose of oral aprepitant 40 or 125 mg (administered with 50 mL of water 1–3 hours before anaesthesia), or an intravenous dose of ondansetron 4 mg (administered immediately before induction of anaesthesia). **VRS** = verbal rating score; an 11-point scale ranging from no nausea (0) to nausea as bad as it could be (10); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs ondansetron.

geographical regions because of differences in healthcare systems, medical practice and unit costs.

## 6. Tolerability

### 6.1 CINV

The tolerability of an antiemetic regimen containing oral aprepitant (125 mg on day 1 then 80 mg once daily on days 2 and 3) has been investigated in patients receiving single or multiple cycles of HEC or MEC who participated in the clinical trials discussed in section 4. Aprepitant was administered in combination with ondansetron and dexamethasone (see table V and table VI for further details). Pooled analyses of the trials[6,13,35] (including those reported in the manufacturer's US prescribing information[6] and the EU summary of product characteristics[13]) are also discussed in this section.

#### *6.1.1 Highly Emetogenic Chemotherapy*

An aprepitant regimen was generally well tolerated in patients receiving a single cycle of HEC (cisplatin based), with most adverse events being mild to moderate in intensity.[6,27-29] The incidence of adverse events in recipients of an aprepitant regimen was similar to that in recipients of the control regimen (dexamethasone plus ondansetron).

According to a combined analysis[6,35] of two well controlled trials[27,28] in patients receiving one cycle of HEC, drug-related clinical adverse events were reported in ≈17% of the 544 recipients of the aprepitant regimen and ≈13% of the 550 recipients of the control regimen. Treatment was discontinued due to a clinical adverse event in 8% of patients treated with the aprepitant regimen and 6% of patients treated with the control regimen.[35] The adverse events that were reported in ≥10% of recipients of aprepitant were asthenia/fatigue, nausea, hiccups, constipation, diarrhoea and anorexia (see figure 4).

© 2009 Adis Data Information BV. All rights reserved.

Serious adverse events were reported in 13% and 14% of recipients of the aprepitant or control regimen.[35] Serious adverse events (regardless of causality) that were reported in the two studies included bradycardia, disorientation and perforated duodenal ulcer.[6]

Laboratory adverse events that occurred in ≥3% of recipients of the aprepitant or control regimen included increases in ALT (6% vs 4.3%), increases in AST (3.0% vs 1.3%), increases in blood urea nitrogen (4.7% vs 3.5%), increases in serum creatinine (3.7% vs 4.3%) and proteinuria (6.8% vs 5.3%).[6] The adverse experiences associated with the increases in ALT or AST were generally mild or moderate in intensity.

The tolerability profiles of an aprepitant regimen and a control regimen during the multiple-cycle extension (up to five additional cycles of chemotherapy) were generally similar to those observed after one cycle of HEC.[13] Drug-related clinical adverse events occurred in 6% and 4% of recipients of the aprepitant (n = 413) or control (n = 438) regimens during cycles 2–6.[36]

#### *6.1.2 Moderately Emetogenic Chemotherapy*

An aprepitant regimen was generally well tolerated in a studies in 866 evaluable patients with breast cancer[30] or 848 evaluable patients with various malignancies[31] receiving a single cycle of MEC.

The adverse event profile of an aprepitant regimen in patients receiving MEC was generally similar to that reported in patients receiving HEC. In recipients of an aprepitant regimen or a control regimen, the incidence of drug-related adverse events was 21.5% and 19.6% in the study

**Table XI.** Cost effectiveness of an aprepitant (APR) regimen (APR plus dexamethasone plus ondansetron) compared with a control (CON) regimen (dexamethasone plus ondansetron) in the prevention of chemotherapy-induced nausea and vomiting. Dosages of the agents involved in these regimens are presented in table V (highly emetogenic chemotherapy [HEC]) and table VI (moderately emetogenic chemotherapy [MEC]). All analyses are from a healthcare payer perspective

| | Lordick et al.[44] | Annemans et al.[45] | Moore et al.[46] |
|---|---|---|---|
| **Methodology** | | | |
| Chemotherapy type | HEC | HEC; MEC | HEC |
| Source of efficacy data | Clinical trials[27,28,36] | HEC[29] and MEC[40] clinical trials (trial-based); longitudinal hospital database (real-life based) | Clinical trial[27] |
| Time horizon | 5 days after a single cycle of chemotherapy | Four cycles (21 days) of chemotherapy | Five cycles (28-day) of chemotherapy |
| Discounting | Undiscounted | NR | NR |
| Study design | Decision analytical | Decision analytical | Markov |
| Year of costing | 2004 | 2005 | 2005 |
| Country of study | Germany | Belgium | US |
| Costs | Physician and hospitalization; antiemetic prophylaxis; rescue medication; unit costs for Germany were applied | Physician and hospitalization; antiemetic prophylaxis; rescue medication; unit costs for Germany were used and then adapted for Belgium | Clinic visit; laboratory costs antiemetic prophylaxis; rescue medication; unit costs for US were used |
| **Incremental results (APR vs CON)** | | | |
| QALYs gained HEC | 0.0017 | 0.003 (trial-based and real-life based) | 0.007 |
| QALYs gained MEC | | 0.014 (trial-based and real-life based) | |
| Costs HEC | €49.60 | –€66.84 (trial-based) and –€74.62 (real-life based) | $US682 |
| Costs MEC | | –€17.95 (trial-based) and –€21.70 (real-life based) | |
| Cost per QALY gained | €28 891 | APR is dominant to CON for HEC and MEC (trial-based and real-life based) | $US97 429 |

**NR** = not reported; **QALY** = quality-adjusted life-year.

© 2009 Adis Data Information BV. All rights reserved.

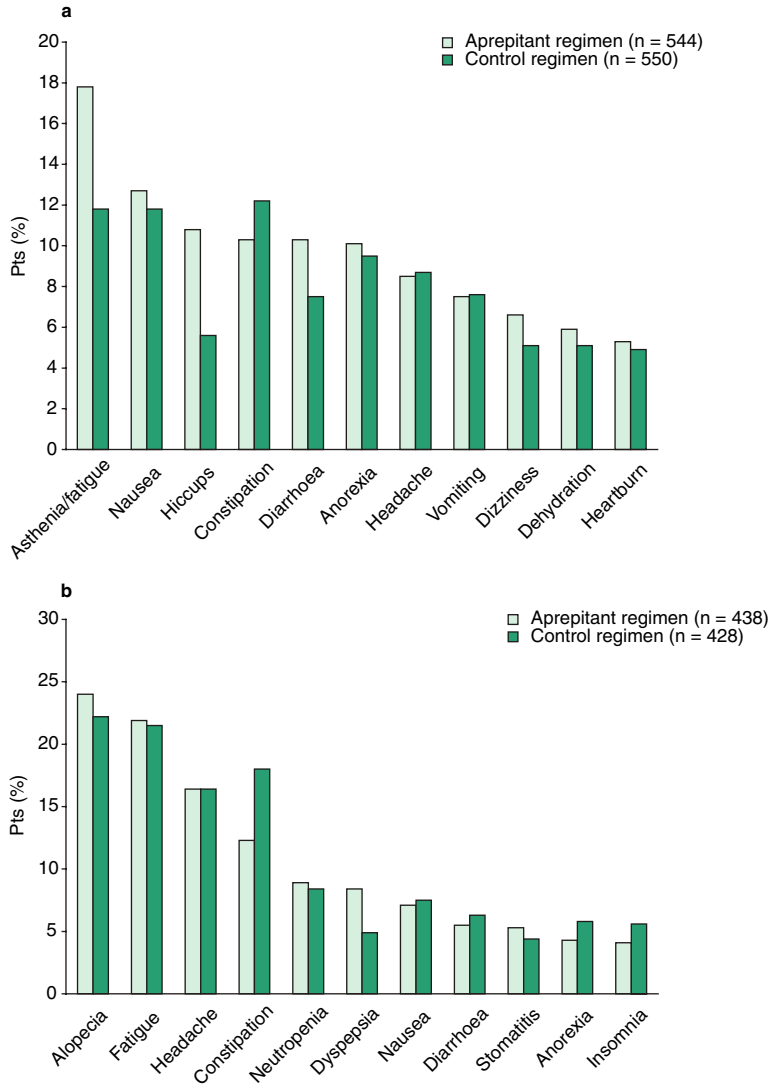


**Fig. 4.** Tolerability of an aprepitant regimen in patients (pts) treated with one cycle of emetogenic chemotherapy. Pts received a control regimen (ondansetron plus dexamethasone) or an aprepitant regimen (aprepitant plus ondansetron plus dexamethasone). Placebo tablets or capsules were administered to maintain blinding. Adverse events reported in ≥5% of either treatment regimen are shown. Nausea or vomiting were considered to be adverse events if they occurred after day 5 of the study or at any time if they were serious, drug related or resulted in discontinuation. Data were obtained from the manufacturer's US prescribing information.[6] Statistical analyses not reported. (**a**) A pooled analysis of two randomized, double-blind, multicentre trials in 1094 evaluable cancer pts treated with highly emetogenic (cisplatin-based) chemotherapy.[6] See table V for further details of dosage and days of administration of each antiemetic agent. (**b**) A randomized, double-blind, multicentre trial in 866 evaluable pts with breast cancer receiving moderately emetogenic chemotherapy.[6] See table VI for further details of dosage and days of administration of each antiemetic agent.

involving breast cancer patients,[30] and 7.2% and 9.3% in the study involving of the patients with various malignancies.[31] Most adverse events were mild to moderate in intensity. Less than 5% of patients reported serious adverse events, with the incidence being similar with the aprepitant or control regimen.[30] The incidences of discontinuations due to adverse events were 1.6%

© 2009 Adis Data Information BV. All rights reserved.

and 1.2% in the study involving patients with breast cancer,[30] and 0.2% and 0.5% in the study involving patients with various cancers.[31]

Adverse events that were reported in ≥5% of recipients of aprepitant included alopecia, fatigue, headache, constipation and dyspepsia,[30,31] with the incidence of these adverse events generally being similar to that in the control regimen (see figure 4 for the aprepitant tolerability profile in patients with breast cancer). In the trial in patients with breast cancer,[6] laboratory adverse events that occurred in ≥3% of recipients of the aprepitant or control regimen included decreases in haemoglobin (2.3% vs 4.7%) and decreases in white blood cell count (9.3% vs 9.0%).

The tolerability profiles of an aprepitant regimen and a control regimen during the multiple-cycle extension study[40] in patients with breast cancer (n = 744) administered up to five additional cycles of MEC were generally similar to those observed after one cycle of MEC.

### 6.2 PONV

The tolerability of a single oral dose of aprepitant 40 mg has been compared with that of a single intravenous dose of ondansetron in patients undergoing open, abdominal surgery who participated in two large, well controlled studies discussed in section 4.[41,42] Tolerability data have also been obtained from the pooled analyses of these trials reported in the aprepitant manufacturer's US prescribing information[6] and the EU summary of product characteristics.[13] In the combined analysis, 564 evaluable patients were administered aprepitant 40 mg and 538 evaluable patients were administered ondansetron 4 mg.

Drug-related clinical adverse experiences were reported in 6% of the aprepitant 40 mg recipients and 4% of the ondansetron recipients.[41,42] Most adverse events were mild to moderate in intensity. According to the combined analysis,[6] the tolerability profiles of aprepitant 40 mg and ondansetron 4 mg were similar, with the most commonly occurring adverse events (≥5% of patients) being constipation (8.5% vs 7.6%), nausea (8.5% vs 8.6%), pruritus (7.6% vs 8.4%), pyrexia (5.9% vs 10.6%), hypotension (5.7% vs 4.6%), headache (5.0% vs 6.5%) and flatulence (4.1% vs 5.8%). A laboratory adverse event that occurred in ≥3% of patients was a decrease in haemoglobin (3.8% vs 4.2%). Increases in ALT were reported in 1.1% of recipients of aprepitant 40 mg and 1.0% of recipients of ondansetron 4 mg.

## 7. Dosage and Administration

Aprepitant, in combination with other antiemetics, is indicated in various markets (including the US[6] and Europe[13]):

- for the prevention of nausea and vomiting associated with initial and repeat courses of MEC;
- for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC (including high-dose cisplatin);
- for the prevention of PONV.

Aprepitant is not recommended for use in paediatric patients, as safety and efficacy have not been established in this population.[6,13] Aprepitant should not be given to pregnant patients unless its use is considered essential. Aprepitant is excreted in the milk of rats; however, it is not known if this agent is excreted in human milk. The US prescribing information notes that the decision as to whether to discontinue nursing or discontinue the aprepitant in nursing mothers should take into account the importance of the drug for the mother and the potential for serious adverse events in nursing infants and its potential for tumorigenicity in animal studies.[6] In Europe, breast feeding is not recommended during treatment with aprepitant.[13]

When used for the prevention of CINV, aprepitant should be administered for 3 days as part of a combination antiemetic regimen that includes a corticosteroid and a 5-$HT_3$ receptor antagonist. The recommended oral aprepitant dosage is 125 mg administered 1 hour prior to the initiation of chemotherapy (day 1) and 80 mg on the mornings of days 2 and 3.[6,13]

When used for the prevention of PONV, the recommended oral dose of aprepitant is 40 mg administered within 3 hours prior to anaesthesia.[6,13]

© 2009 Adis Data Information BV. All rights reserved.

Aprepitant should be used with caution when used concomitantly with drugs that are CYP3A4 substrates or inhibitors (see section 3.4).[6,13] Aprepitant should not be coadministered with pimozide, terfenadine, astemizole or cisapride. Concomitant corticosteroid dosages should be adjusted (see section 3.4). Weak inhibition of CYP3A4 by a single dose of aprepitant 40 mg is not expected to alter the plasma levels of concomitantly administered agents that are primarily metabolized through CYP3A4. The efficacy of aprepitant may be reduced when coadministered by drugs that are strongly induced by CYP3A4. Patients receiving oral contraceptives should use back-up or alternative contraception while they are receiving aprepitant (see section 3.4).

Administration of aprepitant to patients with severe hepatic insufficiency has not been studied; therefore, caution is advised when this agent is administered to this patient group. No dosage adjustment is required in patients with renal insufficiency.[6,13]

The local manufacturer's prescribing information should be consulted for detailed information regarding contraindications, warnings, drug interactions, patient monitoring recommendations and use in special patient populations.

## 8. The Place of Aprepitant in the Prevention of Nausea and Vomiting

Nausea and vomiting cause significant problems in patients recovering from surgical procedures carried out under general anaesthesia and in cancer patient receiving MEC or HEC. Benefits in terms of patients' recovery and health-related quality of life would be achieved with reductions in the incidence of CINV or PONV.[47]

To provide the greatest protection, antiemetic therapy should usually be administered prior to the administration of chemotherapy or prior to surgery. When used in the prevention of CINV, the antiemetic regimen should be continued for the duration of the effect of the chemotherapy involved.[4] Since no single agent can be expected to provide complete protection against the various phases of CINV, a combination of antiemetic agents is usually administered.

Before the advent of 5-$HT_3$ receptor antagonists, available antiemetics included phenothiazines, substituted benzamides, antihistamines, butyrophenones, corticosteroids, benzodiazepines and cannabinoids.[1,4] The introduction of 5-$HT_3$ receptor antagonists represented a major advance in the prevention of CINV and PONV.[1,4,48] These agents (see table XII) have been effective in controlling acute nausea and/or vomiting and are generally well tolerated, and their inclusion in a regimen aimed at preventing acute CINV is recommended (table XIII).[1] Although the first generation of 5-$HT_3$ receptor antagonists (including ondansetron, granisetron and dolasetron) are not generally effective in preventing delayed emesis, the second-generation 5-$HT_3$ receptor antagonist palonosetron has been effective in preventing acute CINV (during the first 24 hours following chemotherapy), and also exhibits prolonged efficacy to provide protection from CINV in the delayed and overall phases.[49,50] Oral forms of 5-$HT_3$ receptor antagonists are as effective as intravenous forms.

Corticosteroids (especially dexamethasone) are effective in the prevention of CINV.[4,51-53] The precise mechanism of action of corticosteroids in the prevention of emesis is uncertain but may involve a reduction of serotonin release or activation of corticosteroid receptors in the CNS.[54] Short-term corticosteroid therapy is generally well tolerated. Dexamethasone is effective in preventing acute and delayed nausea and vomiting and is included in most recommended preventive regimens (table XIII).

**Table XII.** Antiemetic agents

| Class | Examples |
|---|---|
| Benzodiazepines | Lorazepam; olanzapine |
| Cannabinoids | Dronabinol; nabilone |
| Corticosteroids | Dexamethasone; methylprednisolone |
| Dopamine antagonists | Droperidol; haloperidol; metoclopramide; prochlorperazine; promethazine |
| Neurokinin-1 receptor antagonists | Aprepitant; fosaprepitant |
| Serotonin 5-$HT_3$ receptor antagonists | Dolasetron; granisetron; ondansetron; palonosetron; ramosetron and tropisetron |

© 2009 Adis Data Information BV. All rights reserved.

**Table XIII.** Guideline recommendations for the prevention of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) in adult patients (pts). CINV guidelines for highly emetic chemotherapy (HEC) and moderately emetic chemotherapy (MEC) are presented from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC) and National Comprehensive Cancer Network (NCCN). Consensus PONV guidelines from the Society for Ambulatory Anesthesia (SAMBA) are also presented

| Guideline | Recommendation regimen[a] | |
|---|---|---|
| | Day 1 | Day 2 onwards |
| **CINV (HEC)** | | |
| ASCO[52] | APR + DEX + 5-$HT_3$ RA | APR + DEX |
| ESMO[60] | APR + COR + 5-$HT_3$ RA | APR + COR |
| MASCC[61] | APR[b] + DEX + 5-$HT_3$ RA | APR + DEX |
| NCCN[4] | APR[b] + DEX + 5-$HT_3$ RA[c] | APR + DEX ± LOR |
| **CINV (MEC)** | | |
| ASCO[52] | APR[d] + DEX + 5-$HT_3$ RA | APR ± DEX[d]; or DEX |
| ESMO[60] | APR[d] + COR[e] + 5-$HT_3$ RA | APR + DEX[d]; or COR[f]; or 5-$HT_3$ RA[f] |
| MASCC[61] | APR[d] + DEX + 5-$HT_3$ RA | APR + DEX[d]; or DEX[f]; or 5-$HT_3$ RA[f] |
| NCCN[4] | APR[b,g] + DEX + 5-$HT_3$ RA[c] | APR ± DEX[h]; or DEX; or 5-$HT_3$ RA[c] |
| **PONV** | | |
| SAMBA[62] | Combination of ≥1 (moderate risk) or ≥2 (high risk) antiemetic agents from different classes[i] | Another class of drugs[j] |

a See guidelines for recommended dosage of each agent in pts receiving HEC or MEC.

b Intravenous fosaprepitant may be substituted for APR on day 1.

c LOR + histamine receptor antagonist or a proton pump inhibitor are recommended, but optional, additions.

d Pts treated with an anthracycline plus cyclophosphamide only.

e DEX is recommended in pts treated with APR.

f Pts treated with MEC other than anthracycline plus cyclophosphamide.

g In selected pts treated with MEC (e.g. carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate).

h In pts treated with APR on day 1.

i Recommended agents include 5-$HT_3$ RA, DEX or droperidol.

j Recommended agents include DEX, droperidol or promethazine, or a 5-$HT_3$ RA for pts who did not receive prophylaxis.

**5-$HT_3$ RA** = serotonin 5-$HT_3$ receptor antagonist; **APR** = aprepitant; **COR** = corticosteroid; **DEX** = dexamethasone; **LOR** = lorazepam.

$NK_1$ receptor antagonists provide a different and complementary mechanism of preventing emesis to other available antiemetics. $NK_1$ receptor antagonists act by blocking the binding of substance P at the $NK_1$ receptor in the brainstem emetic centre and the GI tract. Aprepitant is the first agent in this class to be approved (including the US,[6] Canada and Europe[13]) for use in the prevention of CINV or PONV (see section 7). Aprepitant is poorly soluble in aqueous solutions and therefore is administered orally. An intravenous form of the prodrug of aprepitant (fosaprepitant) has recently been approved by the US FDA and European Medicines Agency as a substitute for oral aprepitant on day 1 of a standard CINV prevention regimen.[13,55,56] Fosaprepitant is well tolerated, with a pharmacokinetic study demonstrating its bioequivalence to aprepitant.[57]

Other $NK_1$ receptor antagonists that are under investigation in the prevention of CINV and PONV include vofopitant, casopitant and rolapitant.[58,59]

Treatment guidelines for the prevention of CINV have been published by several organizations including the National Comprehensive Cancer Network (NCCN),[4] the American Society of Clinical Oncology,[52] the European Society for Medical Oncology[60] the Multinational Association of Supportive Care in Cancer[61] (table XIII). For cancer patients receiving HEC, the guidelines generally recommend the administration of 3 days of aprepitant (or a single

© 2009 Adis Data Information BV. All rights reserved.

intravenous dose of the prodrug fosaprepitant) in the antiemetic regimen; a corticosteroid (generally dexamethasone) plus any 5-$HT_3$ receptor antagonist are also recommended agents for inclusion. In cancer patients treated with MEC, current guidelines also recommend the administration of 3 days of aprepitant in selected patients. Some guidelines[52,60,61] restrict the use of this agent to patients to be treated with an anthracycline plus cyclophosphamide but the NCCN guidelines suggesting this agent should also be used in patients to be treated with other chemotherapies of moderate emetic risk (e.g. carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate). If aprepitant (administered over 3 days) is used in patients treated with MEC, then generally the guidelines recommend its use in combination with dexamethasone and a 5-$HT_3$ receptor antagonist.

Comparison of prophylactic regimens in the prevention of CINV or PONV should take into account the effect of rescue medication on either nausea or vomiting. Once rescue medication has been administered, the lack of nausea and/or vomiting may be due to the prophylactic medication, the rescue medication or both. Thus, the trials that investigated the efficacy of aprepitant regimens generally used complete response (no emesis and no rescue medication) as the primary endpoint. Phase III trials have established (using this primary endpoint) that an aprepitant regimen was effective in the prevention of CINV and PONV.

Early studies involving aprepitant demonstrated that the triple combination of aprepitant with a corticosteroid and a 5-$HT_3$ receptor antagonist was more effective than the dual combination of a corticosteroid plus another agent in the prevention of cisplatin-induced emesis.[63,64] Subsequent large, phase III trials in patients with cancer (section 4.1.1) confirmed that aprepitant in combination with ondansetron and dexamethasone was more effective than a regimen of ondansetron and dexamethasone in achieving a complete response in the 5 days after administration of a single cycle of cisplatin-based HEC. Moreover, aprepitant was effective in the achievement of a complete response in both the acute and delayed phases. This preventative efficacy was maintained across multiple cycles of chemotherapy. The addition of aprepitant to a regimen containing ondansetron and dexamethasone significantly reduced the impact of CINV on the daily lives of the patients.

Similarly, aprepitant in combination with ondansetron and dexamethasone was more effective than ondansetron and dexamethasone in achieving a complete response and preventing emesis in the 5 days after administration of a single cycle of MEC in phase III studies involving patients with breast cancer or various malignancies. The advantage of the antiemetic effect of the aprepitant regimen over the control regimen seen after the first cycle of MEC was maintained throughout an additional three cycles in a multiple-cycle extension of the large phase III trial in patients with breast cancer (section 4.1.2).

The control of nausea in patients receiving MEC or HEC remains a significant problem.[2] The role of the 3-day aprepitant regimen in the prevention of nausea is unclear, with data from phase III studies being inconsistent. There was a significant difference between the aprepitant and control regimen in the number of patients with no nausea in the delayed and overall phases (table VII) in one[28] of the identical phase III studies in patients treated with HEC (section 4.1.1). In a phase III trial in breast patients receiving MEC,[30] there was no improvement in nausea when aprepitant was added to dexamethasone plus ondansetron (section 4.1.2). Given their differing mechanism of action, cannabinoids may be useful in chemotherapy-induced nausea;[2] however, trials that investigate the combination of a cannabinoid and aprepitant in the prevention of CINV have yet to be conducted.

Since palonosetron is the only 5-$HT_3$ receptor antagonist that is effective in preventing CINV during both the acute and delayed phases, phase I and II studies have investigated the efficacy of various regimens that combine this agent with aprepitant. An early phase II study found that a regimen of aprepitant (days 1–3) plus dexamethasone (days 1–3) plus palonosetron (day 1) was effective in patients (n = 58) receiving various

© 2009 Adis Data Information BV. All rights reserved. 

moderately to moderate-highly emetogenic chemotherapies (complete response rate 78%).[65] The recent NCCN guidelines recommend the use of palonosetron as the preferred 5-$HT_3$ receptor antagonist (in combination with dexamethasone and aprepitant) in patients receiving HEC.[4] This recommendation was based on the results of a randomized study;[66] however, this study used a higher than recommended dosage of palonosetron and aprepitant was not included. In a pilot study in patients treated with HEC and aprepitant plus dexamethasone (days 1–4) plus palonosetron (day 1), a single dose of aprepitant 125 mg on day 1 displayed similar effectiveness to aprepitant administered as a 125 mg dose on day 1 followed by 80 mg on days 2–3.[67] Moreover, a single-day regimen consisting of oral aprepitant 285 mg plus oral dexamethasone plus intravenous palonosetron was effective (51% overall complete response) in 41 patients with breast cancer receiving MEC.[68] Phase III studies in patients receiving HEC or MEC that investigated the efficacy of a single-day regimen of this three-drug combination are warranted.

An aprepitant regimen compared with a control regimen was considered to be cost effective with regard to the cost per QALY in the prevention of CINV in two European studies, although not according to a US analysis (see section 5). In the European studies, the results were most sensitive to changes in the costs of hospitalization, rescue medication (German study) and the cost of ondansetron (Belgian study). In the US study, sensitivity analysis indicated that the aprepitant regimen may be cost effective relative to the control regimen when rescue medication is costly or where the risk of delayed CINV is high.

A single dose of oral aprepitant 40 mg was as effective as ondansetron in preventing PONV (assessed according to complete response in the 24 hours after surgery) in patients who had undergone general open abdominal surgery in two phase III studies (section 4.2). Aprepitant was significantly more effective than ondansetron at preventing vomiting in the 24 and 48 hours after surgery in both studies ($p < 0.001$). During the 48 hours after surgery, aprepitant compared with ondansetron, delayed the time to the first vomiting episode ($p < 0.001$) in both studies.

Aprepitant is generally well tolerated in patients when used in the prevention of CINV or PONV (section 6). In cancer patients receiving single or multiple cycles of HEC or MEC, the incidence of adverse events in recipients of an aprepitant regimen was similar to that in recipients of the control regimen. Commonly reported adverse events were asthenia/fatigue, nausea, hiccups, constipation, diarrhoea and anorexia. The incidence of adverse events with a single oral dose of aprepitant was similar to that with a single intravenous dose of ondansetron when these agents were used in the prevention of PONV. Commonly reported adverse events were similar to those when an aprepitant regimen was used in the prevention of CINV and included constipation, nausea, pruritus, pyrexia, hypotension, headache and flatulence.

Aprepitant is metabolised by CYP3A4. Moreover, aprepitant is also an inhibitor of CYP3A4 and an inducer of both CYP3A4 and CYP2C9. Consequently, aprepitant can cause a number of drug interactions (see section 3.4). The interactions tend to be more significant when the coadministered drug is administered orally rather than through the intravenous route due to first-pass metabolism. The manufacturer notes that caution should be exercised when aprepitant is coadministered with a number of agents including chemotherapeutic agents, with some drugs being contraindicated due to the interaction potential of aprepitant (see section 3.4 and section 7).

The prevention of nausea and vomiting involves a complex interaction between multiple organs and multiple neurotransmitters. Continued research is needed to provide the most effective antiemetic regimen. Such a regimen is likely to involve a combination of various antiemetic agents with different mechanisms of action. In this regard, research is warranted to clarify the role of aprepitant, when used alone or in combination with various other antiemetic agents, in various clinical situations including bone marrow transplantation, multiple-day chemotherapy regimens and radiotherapy-induced nausea.

In conclusion, when combined with a standard regimen of a corticosteroid (dexamethasone) and a serotonin 5-$HT_3$ receptor antagonist (ondan-

© 2009 Adis Data Information BV. All rights reserved.

setron), oral aprepitant (125 mg on day 1 then 80 mg once daily on days 2 and 3) was effective in the prevention of acute and delayed CINV associated with single or multiple cycles of HEC. This aprepitant regimen was also effective in the prevention of CINV in patients treated with single or multiple doses of MEC. A single oral dose of aprepitant 40 mg administered prior to patients undergoing abdominal surgery was also effective in the prevention of PONV. Aprepitant was generally well tolerated. Aprepitant is a recommended option for the treatment of PONV, and when combined with a corticosteroid and 5-$HT_3$ receptor antagonist is a recommended regimen for the treatment of CINV.

## Disclosure

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

## References

1. Navari RM. Pharmacological management of chemotherapy-induced nausea and vomiting: focus on recent developments. Drugs 2009; 69 (5): 515-33
2. Navari RM. Antiemetic control: toward a new standard of care for emetogenic chemotherapy. Expert Opin Pharmacother 2009 Mar; 10 (4): 629-44
3. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006; 102 (6): 1884-9
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology™ Vol 3 [online]. Available from URL: http://www.nccn.org [Accessed 2009 Jun 30]
5. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. Drugs 2004; 64 (7): 777-94
6. Merck & Co., Inc. EMEND® (aprepitant) capsules: prescribing information. USA [online]. Available from URL: http://www.merck.com [Accessed 2009 Apr 10]
7. Huskey SE, Dean BJ, Bakhtiar R, et al. Brain penetration of aprepitant, a substance P receptor antagonist, in ferrets. Drug Metab Dispos 2003; 31 (6): 785-91
8. Bergström M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. Biol Psychiatry 2004 May 15; 55 (10): 1007-12
9. Hargreaves R. Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. J Clin Psychiatry 2002; 63 Suppl. 11: 18-24
10. Hale JJ, Mills SG, MacCoss M, et al. Structural optimization affording 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonist. J Med Chem 1998 Nov 5; 41 (23): 4607-14
11. Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK1 receptor antagonist MK-0869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 2000 Feb 14; 39 (4): 652-63
12. Madsen JL, Fuglsang S. A randomized, placebo-controlled, crossover, double-blind trial of the NK1 receptor antagonist aprepitant on gastrointestinal motor function in healthy humans. Aliment Pharmacol Ther 2008 Apr 1; 27 (7): 609-15
13. European Medicines Agency. EMEND®: summary of product characteristics [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/emend/H-527-PI-en.pdf [Accessed 2009 Apr 25]
14. Huskey SE, Dean BJ, Doss GA, et al. The metabolic disposition of aprepitant, a substance P receptor antagonist, in rats and dogs. Drug Metab Dispos 2003; 32 (2): 246-58
15. Sanchez RI, Wang RW, Newton DJ, et al. Cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. Drug Metab Dispos 2004 Nov; 32 (11): 1287-92
16. Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer 2009 Feb; 52 (2): 242-7
17. Depré M, Van Hecken A, Oeyen M, et al. Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. Eur J Clin Pharmacol 2005 Jul; 61 (5-6): 341-6
18. Bergman AJ, Marbury T, Fosbinder T, et al. Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. Clin Pharmacokinet 2005; 44 (6): 637-47
19. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003 Jul; 74 (1): 17-24
20. Blum RA, Majumdar A, McCrea J, et al. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. Clin Ther 2003 May; 25: 1407-19
21. Shah AK, Hunt TL, Gallagher SC, et al. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. Curr Med Res Opin 2005 Apr; 21 (4): 595-601
22. Walko CM, Yu AY, Bhushan S, et al. Aprepitant's (AP) effect on cyclophosphamide (CPA) in early breast cancer patients: evaluation of pharmacokinetics [abstract no. 588]. J Clin Oncol 2009; 27 Suppl.: 15s
23. Nygren P, Hande K, Petty KJ, et al. Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. Cancer Chemother Pharmacol 2005 Jun; 55 (6): 609-16
24. Loos WJ, de Wit R, Freedman SJ, et al. Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. Cancer Chemother Pharmacol 2007 Feb; 59 (3): 407-12

© 2009 Adis Data Information BV. All rights reserved. 

25. Feuring M, Lee Y, Orlowski LH, et al. Lack of effect of aprepitant on digoxin pharmacokinetics in healthy subjects. J Clin Pharmacol 2003 Aug; 43 (8): 912-7
26. Lindley CM, Hirsch JD, O'Neill CV, et al. Quality of life consequences of chemotherapy-induced emesis. Qual Life Res 1992 Oct; 1 (5): 331-40
27. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomised, double-blind, placebo-controlled trial in patients receiving high-dose cisplating: the aprepitant protocol 052 study group. J Clin Oncol 2003 Nov 15; 21 (22): 4112-9
28. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor anatagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003 Jun 15; 97 (12): 3090-8
29. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 2006 Jun; 17 (6): 1000-6
30. Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 2005 Apr 20; 23 (12): 2822-30
31. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. Epub 2009 Jul 1
32. Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. Breast Cancer Res Treat 2009 Feb; 113 (3): 529-35
33. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 2003 May 1; 97 (9): 2290-300
34. de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003 Nov 15; 21 (22): 4105-11
35. Warr DG, Grunberg SM, Gralla RJ, et al. The oral NK1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. Eur J Cancer 2005 Jun; 41 (9): 1278-85
36. de Wit R, Herrstedt J, Rapoport B, et al. The oral NK1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. Eur J Cancer 2004; 40: 403-10
37. Gralla RJ, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two phase III randomized clinical trials. Cancer 2005 Aug 15; 104 (4): 864-8
38. Hesketh PJ, Grunberg SM, Herrstedt J, et al. Combined data from phase III trials of the NK1 antagonist aprepitant plus a 5HT3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. Support Care Cancer 2006 Apr 1; 14 (4): 354-60
39. De Wit R, Hesketh PJ, Warr D, et al. The oral NK1 antagonist aprepitant for prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy. Am J Cancer 2005; 4 (1): 35-48
40. Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer 2005 Oct 1; 104 (7): 1548-55
41. Diemunsch P, Gan TJ, Philip BK, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth 2007 Aug; 99 (2): 202-11
42. Gan TJ, Apfel CC, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. Anesth Analg 2007 May; 104 (5): 1082-9
43. Diemunsch P, Apfel C, Gan TJ, et al. Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. Curr Med Res Opin 2007 Oct; 23 (10): 2559-65
44. Lordick F, Ehlken B, Ihbe-Heffinger A, et al. Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer 2007 Jan; 43 (2): 299-307
45. Annemans L, Strens D, Lox E, et al. Cost-effectiveness analysis of aprepitant in the prevention of chemotherapy-induced nausea and vomiting in Belgium. Support Care Cancer 2008 Aug; 16 (8): 905-15
46. Moore S, Tumeh J, Wojtanowski S, et al. Cost-effectiveness of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. Value Health 2007 Jan; 10 (1): 23-31
47. Bloechl-Daum B, Deuson RR, Mavros P, et al. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 2006 Sep 20; 24 (27): 4472-8
48. Gan TJ. Selective serotonin 5-HT3 receptor antagonists for postoperative nausea and vomiting: are they all the same? CNS Drugs 2005; 19 (3): 225-38
49. Siddiqui MAA, Scott LJ. Palonosetron. Drugs 2004; 64 (10): 1125-32
50. Aapro MS. Palonosetron as an anti-emetic and anti-nausea agent in oncology. Ther Clin Risk Manag 2007 Dec; 3 (6): 1009-20
51. Stieler JM, Reichardt P, Riess H, et al. Treatment options for chemotherapy-induced nausea and vomiting: current and future. Am J Cancer 2003; 2 (1): 15-26

© 2009 Adis Data Information BV. All rights reserved. 

52. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006 Jun 20; 24 (18): 2932-47
53. Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol 2000 Oct 1; 18 (19): 3409-22
54. Grunberg SM. Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. Ann Oncol 2007 Feb; 18 (2): 233-40
55. Van Belle SJ, Cocquyt V. Fosaprepitant dimeglumine (MK-0517 or L-785,298), an intravenous neurokinin-1 antagonist for the prevention of chemotherapy induced nausea and vomiting. Expert Opin Pharmacother 2008 Dec; 9 (18): 3261-70
56. Merck & Co., Inc. Emend® (fosaprepitant dimeglumine) for injection [online]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022023s001lbl.pdf [Accessed 2009 Jun 23]
57. Lasseter KC, Gambale J, Jin B, et al. Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. J Clin Pharmacol 2007 Jul; 47 (7): 834-40
58. Diemunsch P, Joshi GP, Brichant JF. Neurokinin 1 receptor antagonists in the prevention of postoperative nausea and vomiting. Br J Anaesth 2009 May 19; 103 (1): 7-13
59. Navari RM. Casopitant, a neurokinin-1 receptor antagonist with anti-emetic and anti-nausea activities. Curr Opin Investig Drugs 2008 Jul; 9 (7): 774-85
60. Herrstedt J, Roila F. Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol 2008 May; 19 Suppl. 2: ii110-2
61. Multinational Association of Supportive Care in Cancer. Perugia International Cancer Conference VII: antiemetic guidelines [online]. Available from URL: http://data.memberclicks.com/site/mascc/MASCC_Guidelines_Update.pdf [Accessed 2008 Jun 22]
62. Gan TJ, Meyer TA, Apfel CC, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007 Dec; 105 (6): 1615-28, table of contents
63. Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001 Mar 15; 19 (6): 1759-67
64. Van Belle S, Lichinitser MR, Navari RM, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. Cancer 2002 Jun 1; 94 (11): 3032-41
65. Grote T, Hajdenberg J, Cartmell A, et al. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. J Support Oncol 2006 Sep; 4 (8): 403-8
66. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 2009 Feb; 10 (2): 115-24
67. Herrington JD, Jaskiewicz AD, Song J. Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Cancer 2008 May 1; 112 (9): 2080-7
68. Grunberg SM, Dugan M, Muss H, et al. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. Support Care Cancer 2009 May; 17 (5): 589-94

Correspondence: *Monique P. Curran,* Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz

© 2009 Adis Data Information BV. All rights reserved. 