ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg hard capsules
EMEND 80 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 125 mg capsule contains 125 mg of aprepitant. Each 80 mg capsule contains 80 mg of aprepitant.

Excipient with known effect
Each capsule contains 125 mg of sucrose (in the 125 mg capsule).
Excipient with known effect
Each capsule contains 80 mg of sucrose (in the 80 mg capsule).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The 125 mg capsule is opaque with a white body and pink cap with "462" and "125 mg" printed radially in black ink on the body. The 80 mg capsules are opaque with a white body and cap with "461" and "80 mg" printed radially in black ink on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12.

EMEND 125 mg/80 mg is given as part of combination therapy (see section 4.2).

4.2 Posology and method of administration

Posology
Adults
EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose is 125 mg orally once daily one hour before start of chemotherapy on Day 1 and 80 mg orally once daily on Days 2 and 3 in the morning.

The following regimens are recommended in adults for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy:

Highly Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3	Day 4
EMEND	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information	none	none	none

Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 to 4. The dose of dexamethasone accounts for active substance interactions.

Moderately Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3
EMEND	125 mg orally	80 mg orally	80 mg orally
Dexamethasone	12 mg orally	none	none
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information	none	none

Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for active substance interactions.

Paediatric population

Adolescents (aged 12 through 17 years)

EMEND is given for 3 days as part of a regimen that includes a 5-HT_3 antagonist. The recommended dose of capsules of EMEND is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. EMEND is administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning. See the Summary of Product Characteristics (SmPC) for the selected 5-HT_3 antagonist for appropriate dosing information. If a corticosteroid, such as dexamethasone, is co-administered with EMEND, the dose of the corticosteroid should be administered at 50 % of the usual dose (see sections 4.5 and 5.1).

The safety and efficacy of the 80 mg and 125 mg capsules have not been demonstrated in children less than 12 years of age. No data are available. Refer to the powder for oral suspension SmPC for appropriate dosing in infants, toddlers and children aged 6 months to less than 12 years.

General

Efficacy data in combination with other corticosteroids and 5-HT_3 antagonists are limited. For additional information on the co-administration with corticosteroids, see section 4.5. Please refer to the SmPC of co-administered 5-HT_3 antagonist medicinal products.

Special populations

Elderly (≥ 65 years)

No dose adjustment is necessary for the elderly (see section 5.2).

Gender

No dose adjustment is necessary based on gender (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment or for patients with end stage renal disease undergoing haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. Aprepitant should be used with caution in these patients (see sections 4.4 and 5.2).

Method of administration
The hard capsule should be swallowed whole.
EMEND may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with pimozide, terfenadine, astemizole or cisapride (see section 4.5).

4.4 Special warnings and precautions for use

Patients with moderate to severe hepatic impairment
There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. EMEND should be used with caution in these patients (see section 5.2).

CYP3A4 interactions
EMEND should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, ergot alkaloid derivatives, fentanyl, and quinidine (see section 4.5). Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination might result in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)
In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely during treatment with EMEND and for 14 days following each 3-day course of EMEND (see section 4.5).

Co-administration with hormonal contraceptives
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of EMEND. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMEND and for 2 months following the last dose of EMEND (see section 4.5).

Excipients
EMEND capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Aprepitant (125 mg/80 mg) is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with EMEND, CYP3A4 is inhibited. After the end of treatment, EMEND causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation.

Aprepitant does not seem to interact with the P-glycoprotein transporter, as suggested by the lack of interaction of aprepitant with digoxin.

Effect aprepitant on the pharmacokinetics of other active substances
CYP3A4 inhibition
As a moderate inhibitor of CYP3A4, aprepitant (125 mg/80 mg) can increase plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of orally administered CYP3A4 substrates may increase up to approximately 3-fold during the 3-day treatment with EMEND; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. EMEND must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride (see section 4.3). Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. Caution is advised during concomitant administration of EMEND and orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see section 4.4).

Corticosteroids
Dexamethasone: The usual oral dexamethasone dose should be reduced by approximately 50 % when co-administered with EMEND 125 mg/80 mg regimen. The dose of dexamethasone in chemotherapy induced nausea and vomiting (CINV) clinical trials was chosen to account for active substance interactions (see section 4.2). EMEND, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and EMEND when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, 2.2-fold on Days 1 and 5.

Methylprednisolone: The usual intravenously administered methylprednisolone dose should be reduced approximately 25 %, and the usual oral methylprednisolone dose should be reduced approximately 50 % when co-administered with EMEND 125 mg/80 mg regimen. EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.3-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was co-administered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

During continuous treatment with methylprednisolone, the AUC of methylprednisolone may decrease at later time points within 2 weeks following initiation of the EMEND dose, due to the inducing effect of aprepitant on CYP3A4. This effect may be expected to be more pronounced for orally administered methylprednisolone.

Chemotherapeutic medicinal products
In pharmacokinetic studies, EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, did not influence the pharmacokinetics of docetaxel administered intravenously on Day 1 or vinorelbine administered intravenously on Day 1 or Day 8. Because the effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates, an interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g., etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolised primarily or partly by CYP3A4 (see section 4.4). Postmarketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration.

Immunosuppressants
During the 3-day CINV regimen, a transient moderate increase followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g., cyclosporine, tacrolimus, everolimus and sirolimus) is expected. Given the short duration of the 3-day regimen and the time-dependent limited changes in exposure, dose reduction of the immunosuppressant is not recommended during the 3 days of co-administration with EMEND.

Midazolam
The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicinal products with EMEND (125 mg/80 mg).

EMEND increased the AUC of midazolam, a sensitive CYP3A4 substrate, 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of 2 mg midazolam was co-administered on Days 1 and 5 of a regimen of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 to 5.

In another study with intravenous administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and 2 mg midazolam was given intravenously prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. EMEND increased the AUC of midazolam 25 % on Day 4 and decreased the AUC of midazolam 19 % on Day 8 and 4 % on Day 15. These effects were not considered clinically important.

In a third study with intravenous and oral administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, together with ondansetron 32 mg Day 1, dexamethasone 12 mg Day 1 and 8 mg Days 2-4. This combination (i.e. EMEND, ondansetron and dexamethasone) decreased the AUC of oral midazolam 16 % on Day 6, 9 % on Day 8, 7 % on Day 15 and 17 % on Day 22. These effects were not considered clinically important.

An additional study was completed with intravenous administration of midazolam and EMEND. Intravenous 2 mg midazolam was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. This effect was not considered clinically important.

Induction
As a mild inducer of CYP2C9, CYP3A4 and glucuronidation, aprepitant can decrease plasma concentrations of substrates eliminated by these routes within two weeks following initiation and treatment. This effect may become apparent only after the end of a 3-day treatment with EMEND. For CYP2C9 and CYP3A4 substrates, the induction is transient with a maximum effect reached 3-5 days after end of the EMEND 3-day treatment. The effect is maintained for a few days, thereafter slowly declines and is clinically insignificant by two weeks after end of EMEND treatment. Mild induction of glucuronidation is also seen with 80 mg oral aprepitant given for 7 days. Data are lacking regarding effects on CYP2C8 and CYP2C19. Caution is advised when warfarin, acenocoumarol, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered during this time period.

Warfarin
In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with EMEND and for 2 weeks following each 3-day course of EMEND for chemotherapy induced nausea and vomiting (see section 4.4). When a single 125 mg dose of EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilised on chronic warfarin therapy, there was no effect of EMEND on the plasma AUC of R(+) or S(-) warfarin determined on Day 3; however, there was a 34 % decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14 % decrease in INR 5 days after completion of treatment with EMEND.

Tolbutamide
EMEND, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23 % on Day 4, 28 % on Day 8, and 15 % on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15.

Hormonal contraceptives
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of EMEND. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMEND and for 2 months following the last dose of EMEND.

In a clinical study, single doses of an oral contraceptive containing ethinyl estradiol and norethindrone were administered on Days 1 through 21 with EMEND, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg intravenously on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. During days 9 through 21 in this study, there was as much as a 64 % decrease in ethinyl estradiol trough concentrations and as much as a 60 % decrease in norethindrone trough concentrations.

5-HT_3 antagonists
In clinical interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of other medicinal products on the pharmacokinetics of aprepitant
Concomitant administration of EMEND with active substances that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, and protease inhibitors) should be approached cautiously, as the combination is expected to result several-fold in increased plasma concentrations of aprepitant (see section 4.4).

Concomitant administration of EMEND with active substances that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy of EMEND. Concomitant administration of EMEND with herbal preparations containing St. John's Wort (*Hypericum perforatum*) is not recommended.

Ketoconazole
When a single 125 mg dose of aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold.

Rifampicin
When a single 375 mg dose of aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampicin, a strong CYP3A4 inducer, the AUC of aprepitant decreased 91 % and the mean terminal half-life decreased 68 %.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of EMEND. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMEND and for 2 months following the last dose of EMEND (see sections 4.4 and 4.5).

Pregnancy
For aprepitant no clinical data on exposed pregnancies are available. The potential for reproductive toxicity of aprepitant has not been fully characterised, since exposure levels above the therapeutic exposure in humans at the 125 mg/80 mg dose could not be attained in animal studies. These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential effects on

reproduction of alterations in neurokinin regulation are unknown. EMEND should not be used during pregnancy unless clearly necessary.

Breast-feeding
Aprepitant is excreted in the milk of lactating rats. It is not known whether aprepitant is excreted in human milk; therefore, breast-feeding is not recommended during treatment with EMEND.

Fertility
The potential for effects of aprepitant on fertility has not been fully characterised because exposure levels above the therapeutic exposure in humans could not be attained in animal studies. These fertility studies did not indicate direct or indirect harmful effects with respect to mating performance, fertility, embryonic/foetal development, or sperm count and motility (see section 5.3).

4.7 Effects on ability to drive and use machines

EMEND may have minor influence on the ability to drive, cycle and use machines. Dizziness and fatigue may occur following administration of EMEND (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The safety profile of aprepitant was evaluated in approximately 6,500 adults in more than 50 studies and 184 children and adolescents in 2 pivotal paediatric clinical trials.

The most common adverse reactions reported at a greater incidence in adults treated with the aprepitant regimen than with standard therapy in patients receiving Highly Emetogenic Chemotherapy (HEC) were: hiccups (4.6 % versus 2.9 %), alanine aminotransferase (ALT) increased (2.8 % versus 1.1 %), dyspepsia (2.6 % versus 2.0 %), constipation (2.4 % versus 2.0 %), headache (2.0 % versus 1.8 %), and decreased appetite (2.0 % versus 0.5 %). The most common adverse reaction reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy in patients receiving Moderately Emetogenic Chemotherapy (MEC) was fatigue (1.4 % versus 0.9 %).

The most common adverse reactions reported at a greater incidence in paediatric patients treated with the aprepitant regimen than with the control regimen while receiving emetogenic cancer chemotherapy were hiccups (3.3 % versus 0.0 %) and flushing (1.1 % versus 0.0 %).

Tabulated list of adverse reactions
The following adverse reactions were observed in a pooled analysis of the HEC and MEC studies at a greater incidence with aprepitant than with standard therapy in adults or paediatric patients or in post-marketing use. The frequency categories given in the table are based on the studies in adults; the observed frequencies in the paediatric studies were similar or lower, unless shown in the table. Some less common ADRs in the adult population were not observed in the paediatric studies.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	Adverse reaction	Frequency
Infection and infestations	candidiasis, staphylococcal infection	rare
Blood and lymphatic system disorders	febrile neutropenia, anaemia	uncommon
Immune system disorders	hypersensitivity reactions including anaphylactic reactions	not known
Metabolism and nutrition disorders	decreased appetite	common
	polydipsia	rare

System organ class	Adverse reaction	Frequency
Psychiatric disorders	anxiety	uncommon
	disorientation, euphoric mood	rare
Nervous system disorders	headache	common
	dizziness, somnolence	uncommon
	cognitive disorder, lethargy, dysgeusia	rare
Eye disorders	conjunctivitis	rare
Ear and labyrinth disorders	tinnitus	rare
Cardiac disorders	palpitations	uncommon
	bradycardia, cardiovascular disorder	rare
Vascular disorders	hot flush/flushing	uncommon
Respiratory, thoracic and mediastinal disorders	hiccups	common
	oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation	rare
Gastrointestinal disorders	constipation, dyspepsia	common
	eructation, nausea[†], vomiting[†], gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence	uncommon
	duodenal ulcer perforation, stomatitis, abdominal distension, faeces hard, neutropenic colitis	rare
Skin and subcutaneous tissue disorders	rash, acne	uncommon
	photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/toxic epidermal necrolysis	rare
	pruritus, urticaria	not known
Musculoskeletal and connective tissue disorders	muscular weakness, muscle spasms	rare
Renal and urinary disorders	dysuria	uncommon
	pollakiuria	rare

System organ class	Adverse reaction	Frequency
General disorders and administration site conditions	fatigue	common
	asthenia, malaise	uncommon
	oedema, chest discomfort, gait disturbance	rare
Investigations	ALT increased	common
	AST increased, blood alkaline phosphatase increased	uncommon
	red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present, urine output increased	rare

†Nausea and vomiting were efficacy parameters in the first 5 days of post-chemotherapy treatment and were reported as adverse reactions only thereafter.

Description of selected adverse reactions
The adverse reactions profiles in adults in the Multiple-Cycle extension of HEC and MEC studies for up to 6 additional cycles of chemotherapy were generally similar to those observed in Cycle 1.

In an additional active-controlled clinical study in 1,169 adult patients receiving aprepitant and HEC, the adverse reactions profile was generally similar to that seen in the other HEC studies with aprepitant.

Non-CINV studies
Additional adverse reactions were observed in adult patients treated with a single 40 mg dose of aprepitant for postoperative nausea and vomiting (PONV) with a greater incidence than with ondansetron: abdominal pain upper, bowel sounds abnormal, constipation*, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, sub-ileus*, visual acuity reduced, wheezing.
*Reported in patients taking a higher dose of aprepitant.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, emesis induced by a medicinal product may not be effective.

Aprepitant cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, ATC code: A04AD12

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK_1) receptors.

3-day regimen of aprepitant in adults

In 2 randomised, double-blind studies encompassing a total of 1,094 adult patients receiving chemotherapy that included cisplatin ≥ 70 mg/m^2, aprepitant in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with a standard regimen (placebo plus ondansetron 32 mg intravenously administered on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4). Although a 32 mg intravenous dose of ondansetron was used in clinical trials, this is no longer the recommended dose. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information.

Efficacy was based on evaluation of the following composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) primarily during Cycle 1. The results were evaluated for each individual study and for the 2 studies combined.

A summary of the key study results from the combined analysis is shown in Table 1.

Table 1
Percent of adult patients receiving Highly Emetogenic Chemotherapy responding by treatment group and phase — Cycle 1

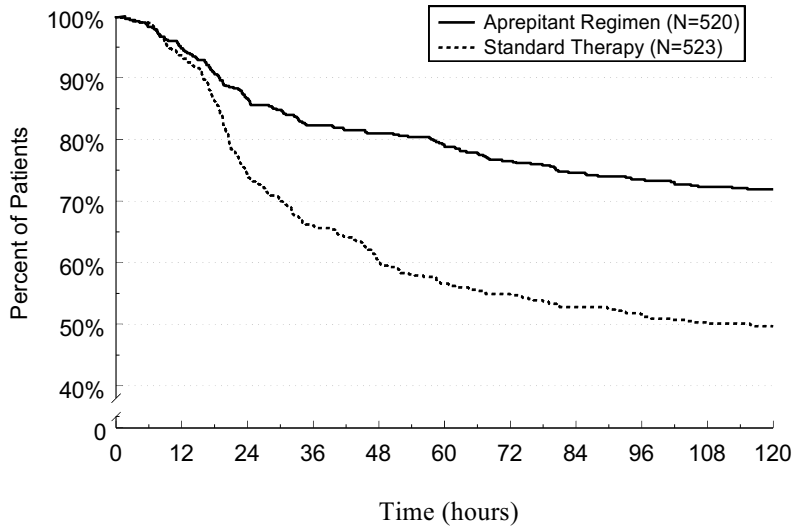
	Aprepitant regimen (N= 521)†	Standard therapy (N= 524)†	Differences*	
COMPOSITE MEASURES	%	%	%	(95 % CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	67.7	47.8	19.9	(14.0, 25.8)
0-24 hours	86.0	73.2	12.7	(7.9, 17.6)
25-120 hours	71.5	51.2	20.3	(14.5, 26.1)
INDIVIDUAL MEASURES				
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	71.9	49.7	22.2	(16.4, 28.0)
0-24 hours	86.8	74.0	12.7	(8.0, 17.5)
25-120 hours	76.2	53.5	22.6	(17.0, 28.2)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	72.1	64.9	7.2	(1.6, 12.8)
25-120 hours	74.0	66.9	7.1	(1.5, 12.6)

* The confidence intervals were calculated with no adjustment for gender and concomitant chemotherapy, which were included in the primary analysis of odds ratios and logistic models.

† One patient in the aprepitant regimen only had data in the acute phase and was excluded from the overall and delayed phase analyses; one patient in the Standard regimen only had data in the delayed phase and was excluded from the overall and acute phase analyses.

The estimated time to first emesis in the combined analysis is depicted by the Kaplan-Meier plot in Figure 1.

Figure 1
Percent of adult patients receiving Highly Emetogenic Chemotherapy
who remain emesis free over time – Cycle 1



Statistically significant differences in efficacy were also observed in each of the 2 individual studies.

In the same 2 clinical studies, 851 adult patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was apparently maintained during all cycles.

In a randomised, double-blind study in a total of 866 adult patients (864 females, 2 males) receiving chemotherapy that included cyclophosphamide 750-1,500 mg/m^2; or cyclophosphamide 500-1,500 mg/m^2 and doxorubicin ($\leq$ 60 mg/m^2) or epirubicin ($\leq$ 100 mg/m^2), aprepitant in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with standard therapy (placebo plus ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1).

Efficacy was based on evaluation of the composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) primarily during Cycle 1.

A summary of the key study results is shown in Table 2.

Table 2
Percent of adult patients responding by treatment group and phase — Cycle 1
Moderately Emetogenic Chemotherapy

COMPOSITE MEASURES	Aprepitant regimen (N= 433)† %	Standard therapy (N= 424) %	Differences* %	(95 % CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	50.8	42.5	8.3	(1.6, 15.0)
0-24 hours	75.7	69.0	6.7	(0.7, 12.7)
25-120 hours	55.4	49.1	6.3	(-0.4, 13.0)
INDIVIDUAL MEASURES				
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	75.7	58.7	17.0	(10.8, 23.2)
0-24 hours	87.5	77.3	10.2	(5.1, 15.3)
25-120 hours	80.8	69.1	11.7	(5.9, 17.5)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	60.9	55.7	5.3	(-1.3, 11.9)
0-24 hours	79.5	78.3	1.3	(-4.2, 6.8)
25-120 hours	65.3	61.5	3.9	(-2.6, 10.3)

* The confidence intervals were calculated with no adjustment for age category (< 55 years, ≥ 55 years) and investigator group, which were included in the primary analysis of odds ratios and logistic models.
† One patient in the aprepitant regimen only had data in the acute phase and was excluded from the overall and delayed phase analyses.

In the same clinical study, 744 adult patients continued into the Multiple-Cycle extension for up to 3 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was apparently maintained during all cycles.

In a second multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 adult patients (652 females, 196 males) receiving a chemotherapy regimen that included any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide intravenously (< 1,500 mg/m^2); or cytarabine intravenously (> 1 g/m^2). Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumour types including 52 % with breast cancer, 21 % with gastrointestinal cancers including colorectal cancer, 13 % with lung cancer and 6 % with gynaecological cancers. The aprepitant regimen in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with standard therapy (placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1).

Efficacy was based on the evaluation of the following primary and key secondary endpoints: No vomiting in the overall period (0 to 120 hours post-chemotherapy), evaluation of safety and tolerability of the aprepitant regimen for chemotherapy induced nausea and vomiting (CINV), and complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy). Additionally, no significant nausea in the overall period (0 to 120 hours post-chemotherapy) was evaluated as an exploratory endpoint, and in the acute and delayed phases as a post-hoc analysis.

A summary of the key study results is shown in Table 3.

Table 3
Percent of adult patients responding by treatment group and phase for Study 2 – Cycle 1
Moderately Emetogenic Chemotherapy

	Aprepitant regimen (N= 425) %	Standard therapy (N= 406) %	Differences* %	(95 % CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	68.7	56.3	12.4	(5.9, 18.9)
0-24 hours	89.2	80.3	8.9	(4.0, 13.8)
25-120 hours	70.8	60.9	9.9	(3.5, 16.3)
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	76.2	62.1	14.1	(7.9, 20.3)
0-24 hours	92.0	83.7	8.3	(3.9, 12.7)
25-120 hours	77.9	66.8	11.1	(5.1, 17.1)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	73.6	66.4	7.2	(1.0, 13.4)
0-24 hours	90.9	86.3	4.6	(0.2, 9.0)
25-120 hours	74.9	69.5	5.4	(-0.7, 11.5)

* The confidence intervals were calculated with no adjustment for gender and region, which were included in the primary analysis using logistic models.

The benefit of aprepitant combination therapy in the full study population was mainly driven by the results observed in patients with poor control with the standard regimen such as in women, even though the results were numerically better regardless of age, tumour type or gender. Complete response to the aprepitant regimen and standard therapy, respectively, was reached in 209/324 (65 %) and 161/320 (50 %) in women and 83/101 (82 %) and 68/87 (78 %) of men.

Paediatric population

In a randomised, double-blind, active comparator-controlled clinical study that included 302 children and adolescents (aged 6 months to 17 years) receiving moderately or highly emetogenic chemotherapy, the aprepitant regimen was compared to a control regimen for the prevention of CINV. The efficacy of the aprepitant regimen was evaluated in a single cycle (Cycle 1). Patients had the opportunity to receive open-label aprepitant in subsequent cycles (Optional Cycles 2-6); however efficacy was not assessed in these optional cycles. The aprepitant regimen for adolescents aged 12 through 17 years (n=47) consisted of EMEND capsules 125 mg orally on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron on Day 1. The aprepitant regimen for children aged 6 months to less than 12 years (n=105) consisted of EMEND powder for oral suspension 3.0 mg/kg (up to 125 mg) orally on Day 1 and 2.0 mg/kg (up to 80 mg) orally on Days 2 and 3 in combination with ondansetron on Day 1. The control regimen in adolescents aged 12 through 17 years (n=48) and children aged 6 months to less than 12 years (n=102) consisted of placebo for aprepitant on Days 1, 2 and 3 in combination with ondansetron on Day 1. EMEND or placebo and ondansetron were administered 1 hour and 30 minutes prior to initiation of chemotherapy, respectively. Intravenous dexamethasone was permitted as part of the antiemetic regimen for paediatric patients in both age groups, at the discretion of the physician. A dose reduction (50 %) of dexamethasone was required for paediatric patients receiving aprepitant. No dose reduction was required for paediatric patients receiving the control regimen. Of the paediatric patients, 29 % in the aprepitant regimen and 28 % in the control regimen used dexamethasone as part of the regimen in Cycle 1.

The antiemetic activity of EMEND was evaluated over a 5-day (120 hour) period following the initiation of chemotherapy on Day 1. The primary endpoint was complete response in the delayed phase (25 to 120 hours following initiation of chemotherapy) in Cycle 1. A summary of the key study results are shown in Table 4.

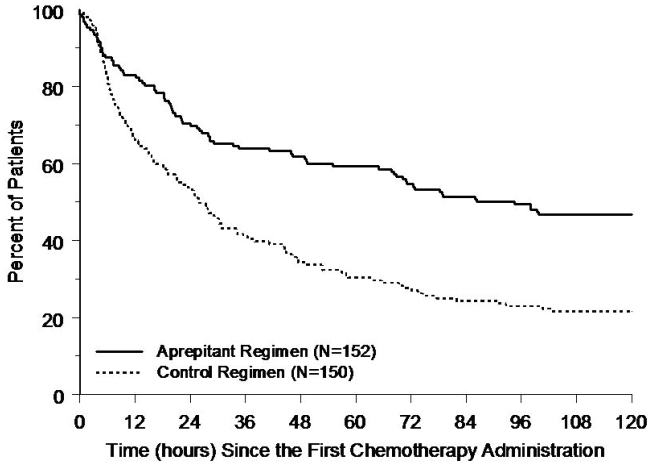
Table 4
Number (%) of paediatric patients with complete response and no vomiting by treatment group and phase – Cycle 1 (Intent to treat population)

	Aprepitant regimen n/m (%)	Control regimen n/m (%)
PRIMARY ENDPOINT		
Complete response* – Delayed phase	77/152 (50.7)†	39/150 (26.0)
OTHER PRESPECIFIED ENDPOINTS		
Complete response* – Acute phase	101/152 (66.4)‡	78/150 (52.0)
Complete response* – Overall phase	61/152 (40.1)†	30/150 (20.0)
No vomiting§ – Overall phase	71/152 (46.7)†	32/150 (21.3)

*Complete response = No vomiting or retching or dry heaves and no use of rescue medication.
†$p < 0.01$ when compared to control regimen.
‡$p < 0.05$ when compared to control regimen.
§No vomiting = No vomiting or retching or dry heaves.
n/m = Number of patients with desired response/number of patients included in time point.
Acute phase: 0 to 24 hours following initiation of chemotherapy.
Delayed phase: 25 to 120 hours following initiation of chemotherapy.
Overall phase: 0 to 120 hours following initiation of chemotherapy.

The estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen (estimated median time to first vomiting was 94.5 hours) compared with the control regimen group (estimated median time to first vomiting was 26.0 hours) as depicted in the Kaplan-Meier curves in Figure 2.

Figure 2
Time to first vomiting episode from start of chemotherapy administration - paediatric patients in the overall phase-Cycle 1 (Intent to treat population)



An analysis of efficacy in subpopulations in Cycle 1 demonstrated that, regardless of age category, gender, use of dexamethasone for antiemetic prophylaxis, and emetogenicity of chemotherapy, the aprepitant regimen provided better control than the control regimen with respect to the complete response endpoints.

5.2 Pharmacokinetic properties

Aprepitant displays non-linear pharmacokinetics. Both clearance and absolute bioavailability decrease with increasing dose.

Absorption
The mean absolute oral bioavailability of aprepitant is 67 % for the 80 mg capsule and 59 % for the 125 mg capsule. The mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (t_{max}). Oral administration of the capsule with an approximately 800 Kcal standard breakfast resulted in an up to 40 % increase in AUC of aprepitant. This increase is not considered clinically relevant.

The pharmacokinetics of aprepitant is non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26 % greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state.

Following oral administration of a single 125 mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} (mean±SD) was 19.6 ± 2.5 µg•h/mL and 21.2 ± 6.3 µg•h/mL on Days 1 and 3, respectively. C_{max} was 1.6 ± 0.36 µg/mL and 1.4 ± 0.22 µg/mL on Days 1 and 3, respectively.

Distribution
Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 66 L in humans.

Biotransformation
Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 19 % of the radioactivity in plasma over 72 hours following a single intravenous administration 100-mg dose of [^{14}C]-fosaprepitant, a prodrug for aprepitant, indicating a substantial presence of metabolites in the plasma. Twelve metabolites of aprepitant have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains and the resultant metabolites were only weakly active. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 and potentially with minor contribution by CYP1A2 and CYP2C19.

Elimination
Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. Following a single intravenously administered 100 mg dose of [^{14}C]-fosaprepitant, a prodrug for aprepitant, to healthy subjects, 57 % of the radioactivity was recovered in urine and 45 % in faeces.

The plasma clearance of aprepitant is dose-dependent, decreasing with increased dose and ranged from approximately 60 to 72 mL/min in the therapeutic dose range. The terminal half-life ranged from approximately 9 to 13 hours.

Pharmacokinetics in special populations
Elderly: Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the AUC_{0-24hr} of aprepitant was 21 % higher on Day 1 and 36 % higher on Day 5 in elderly (≥ 65 years) relative to younger adults. The C_{max} was 10 % higher on Day 1 and 24 % higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dose adjustment for EMEND is necessary in elderly patients.

Gender: Following oral administration of a single 125 mg dose of aprepitant, the C_{max} for aprepitant is 16 % higher in females as compared with males. The half-life of aprepitant is 25 % lower in females as compared with males and its t_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dose adjustment for EMEND is necessary based on gender.

Hepatic impairment: Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a clinically relevant extent. No dose adjustment is necessary for patients with mild hepatic impairment. Conclusions regarding the influence of moderate hepatic impairment (Child-Pugh class B) on aprepitant pharmacokinetics cannot be drawn from available data.

There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment: A single 240 mg dose of aprepitant was administered to patients with severe renal impairment (CrCl < 30 mL/min) and to patients with end stage renal disease (ESRD) requiring haemodialysis.

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21 % and C_{max} decreased by 32 %, relative to healthy subjects. In patients with ESRD undergoing haemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42 % and C_{max} decreased by 32 %. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound aprepitant was not significantly affected in patients with renal impairment compared with healthy subjects. Haemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2 % of the dose was recovered in the dialysate.

No dose adjustment for EMEND is necessary for patients with renal impairment or for patients with ESRD undergoing haemodialysis.

Paediatric population: As part of a 3-day regimen, dosing of aprepitant capsules (125/80/80-mg) in adolescent patients (aged 12 through 17 years) achieved an AUC_{0-24hr} above 17 µg•hr/mL on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.4 µg/mL in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.3 µg/mL on Day 1, occurring at approximately 4 hours. As part of a 3-day regimen, dosing of aprepitant powder for oral suspension (3/2/2-mg/kg) in patients aged 6 months to less than 12 years achieved an AUC_{0-24hr} above 17 µg•hr/mL on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.1 µg/mL in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.2 µg/mL on Day 1, occurring between 5 and 7 hours.

A population pharmacokinetic analysis of aprepitant in paediatric patients (aged 6 months through 17 years) suggests that gender and race have no clinically meaningful effect on the pharmacokinetics of aprepitant.

Relationship between concentration and effect
Using a highly specific NK_1-receptor tracer, positron emission tomography (PET) studies in healthy young men have shown that aprepitant penetrates into the brain and occupies NK_1 receptors in a dose- and plasma-concentration-dependent manner. Aprepitant plasma concentrations achieved with the 3-day regimen of EMEND in adults are predicted to provide greater than 95 % occupancy of brain NK_1 receptors.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. However, it should be noted that systemic exposure in rodents was similar or even lower than therapeutic exposure in humans at the 125 mg/80 mg dose. In particular, although no adverse effects were noted in reproduction studies at human exposure levels, the animal exposures are not sufficient to make an adequate risk assessment in man.

In a juvenile toxicity study in rats treated from postnatal day 10 to day 63 aprepitant led to an earlier vaginal opening in females from 250 mg/kg b.i.d. and to a delayed preputial separation in males, from 10 mg/kg b.i.d. There were no margins to clinically relevant exposure. There were no treatment-related effects on mating, fertility or embryonic/foetal survival, and no pathological changes in the reproductive organs. In a juvenile toxicity study in dogs treated from postnatal day 14 to day 42, a decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and oedema of vaginal tissues were seen in females from 4 mg/kg/day. There were no margins to clinically relevant exposure of aprepitant. For

short term treatment according to recommended dose regimen these findings are considered unlikely to be clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sucrose
Microcrystalline cellulose (E 460)
Hydroxypropylcellulose (E 463)
Sodium laurilsulfate

Capsule shell (125 mg)
Gelatin
Titanium dioxide (E 171)
Red iron oxide (E 172)
Yellow iron oxide (E 172)

Capsule shell (80 mg)
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac
Potassium hydroxide
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

4 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Different pack sizes including different strengths are available.

Aluminium blister containing one 80 mg capsule.
Aluminium blister containing two 80 mg capsules.
5 Aluminium blisters each containing one 80 mg capsule.

Aluminium blister containing one 125 mg capsule.
5 Aluminium blisters each containing one 125 mg capsule.

Aluminium blister containing one 125 mg capsule and two 80 mg capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/03/262/001
EU/1/03/262/002
EU/1/03/262/003
EU/1/03/262/004
EU/1/03/262/005
EU/1/03/262/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 11 November 2003
Date of latest renewal: 22 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 125 mg of aprepitant. After reconstitution, 1 mL oral suspension contains 25 mg of aprepitant.

Excipients with known effect
Each sachet contains approximately 125 mg of sucrose and 468.7 mg lactose (as anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

Pink to light pink powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in children, toddlers and infants from the age of 6 months to less than 12 years.

EMEND powder for oral suspension is given as part of combination therapy (see section 4.2).

4.2 Posology and method of administration

The oral suspension should be prepared and the dose measured by healthcare professionals only.

Posology
Paediatric population
Infants, toddlers and children (aged 6 months to less than 12 years, and not less than 6 kg)
EMEND is given for 3 days as part of a regimen that includes a 5-HT_3 antagonist. The recommended dose of EMEND powder for oral suspension is based on weight, as specified in the table below. EMEND is administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning. See the Summary of Product Characteristics (SmPC) for the selected 5-HT_3 antagonist for appropriate dosing information. If a corticosteroid, such as dexamethasone, is co-administered with EMEND, the dose of the corticosteroid should be administered at 50 % of the usual dose (see sections 4.5 and 5.1).

Recommended dose of EMEND oral suspension in paediatric patients aged 6 months to less than 12 years

	Day 1	**Day 2**	**Day 3**
EMEND oral suspension 25 mg/mL	3 mg/kg orally Maximum dose 125 mg	2 mg/kg orally Maximum dose 80 mg	2 mg/kg orally Maximum dose 80 mg

The efficacy of the 125 mg powder for oral suspension has not been established in children 12 years of age and older. For adolescents aged 12-17 years, EMEND is available as capsules containing 80 mg, or 125 mg of aprepitant.

The safety and efficacy of EMEND powder for oral suspension in infants below 6 months of age or weighing less than 6 kg has not been established. No data are available.

General
Efficacy data in combination with other corticosteroids and 5-HT_3 antagonists are limited. For additional information on the co-administration with corticosteroids, see section 4.5. Please refer to the SmPC of co-administered 5-HT_3 antagonist medicinal products.

Special populations
Gender
No dose adjustment is necessary based on gender (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment or for patients with end stage renal disease undergoing haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. Aprepitant should be used with caution in these patients (see sections 4.4 and 5.2).

Method of administration
The oral suspension may be taken with or without food.
For details on preparation and administration of the suspension, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with pimozide, terfenadine, astemizole or cisapride (see section 4.5).

4.4 Special warnings and precautions for use

Patients with moderate to severe hepatic impairment
There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. EMEND should be used with caution in these patients (see section 5.2).

CYP3A4 interactions
EMEND should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, ergot alkaloid derivatives, fentanyl, and quinidine (see section 4.5). Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination might result in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)
In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely during treatment with EMEND and for 14 days following each 3-day course of EMEND (see section 4.5).

Co-administration with hormonal contraceptives
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of EMEND. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMEND and for 2 months following the last dose of EMEND (see section 4.5).

Excipients
EMEND powder for oral suspension contains sucrose and lactose. Patients with rare hereditary problems of fructose or galactose intolerance, glucose-galactose malabsorption, total lactase deficiency, or sucrase-isomaltase insufficiency should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aprepitant (125 mg/80 mg) is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with EMEND, CYP3A4 is inhibited. After the end of treatment, EMEND causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation. Aprepitant does not seem to interact with the P-glycoprotein transporter, as suggested by the lack of interaction of aprepitant with digoxin.

Effect of aprepitant on the pharmacokinetics of other active substances
CYP3A4 inhibition
As a moderate inhibitor of CYP3A4, aprepitant (125 mg/80 mg) can increase plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of orally administered CYP3A4 substrates may increase up to approximately 3-fold during the 3-day treatment with EMEND; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. EMEND must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride (see section 4.3). Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. Caution is advised during concomitant administration of EMEND and orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see section 4.4).

Corticosteroids
Dexamethasone: The usual oral dexamethasone dose should be reduced by approximately 50 % when co-administered with EMEND 125 mg/80 mg regimen. The dose of dexamethasone in chemotherapy induced nausea and vomiting (CINV) clinical trials was chosen to account for active substance interactions (see section 4.2). EMEND, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and EMEND when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, 2.2-fold on Days 1 and 5.

Methylprednisolone: The usual intravenously administered methylprednisolone dose should be reduced approximately 25 %, and the usual oral methylprednisolone dose should be reduced approximately 50 % when co-administered with EMEND 125 mg/80 mg regimen. EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.3-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was co-administered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

During continuous treatment with methylprednisolone, the AUC of methylprednisolone may decrease at later time points within 2 weeks following initiation of the EMEND dose, due to the inducing effect of aprepitant on CYP3A4. This effect may be expected to be more pronounced for orally administered methylprednisolone.

Chemotherapeutic medicinal products
In pharmacokinetic studies, EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, did not influence the pharmacokinetics of docetaxel administered intravenously on

Day 1 or vinorelbine administered intravenously on Day 1 or Day 8. Because the effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates, an interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g., etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolised primarily or partly by CYP3A4 (see section 4.4). Postmarketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration.

Immunosuppressants
During the 3-day CINV regimen, a transient moderate increase followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g., cyclosporine, tacrolimus, everolimus and sirolimus) is expected. Given the short duration of the 3-day regimen and the time-dependent limited changes in exposure, dose reduction of the immunosuppressant is not recommended during the 3 days of co-administration with EMEND.

Midazolam
The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicinal products with EMEND (125 mg/80 mg).

EMEND increased the AUC of midazolam, a sensitive CYP3A4 substrate, 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of 2 mg midazolam was co-administered on Days 1 and 5 of a regimen of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 to 5.

In another study with intravenous administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and 2 mg midazolam was given intravenously prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. EMEND increased the AUC of midazolam 25 % on Day 4 and decreased the AUC of midazolam 19 % on Day 8 and 4 % on Day 15. These effects were not considered clinically important.

In a third study with intravenous and oral administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, together with ondansetron 32 mg Day 1, dexamethasone 12 mg Day 1 and 8 mg Days 2-4. This combination (i.e. EMEND, ondansetron and dexamethasone) decreased the AUC of oral midazolam 16 % on Day 6, 9 % on Day 8, 7 % on Day 15 and 17 % on Day 22. These effects were not considered clinically important.

An additional study was completed with intravenous administration of midazolam and EMEND. Intravenous 2 mg midazolam was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. This effect was not considered clinically important.

Induction
As a mild inducer of CYP2C9, CYP3A4 and glucuronidation, aprepitant can decrease plasma concentrations of substrates eliminated by these routes within two weeks following initiation and treatment. This effect may become apparent only after the end of a 3-day treatment with EMEND. For CYP2C9 and CYP3A4 substrates, the induction is transient with a maximum effect reached 3-5 days after end of the EMEND 3-day treatment. The effect is maintained for a few days, thereafter slowly declines and is clinically insignificant by two weeks after end of EMEND treatment. Mild induction of glucuronidation is also seen with 80 mg oral aprepitant given for 7 days. Data are lacking regarding effects on CYP2C8 and CYP2C19. Caution is advised when warfarin, acenocoumarol, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered during this time period.

Warfarin
In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with EMEND and for 2 weeks following each 3-day course of EMEND for

chemotherapy induced nausea and vomiting (see section 4.4). When a single 125 mg dose of EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilised on chronic warfarin therapy, there was no effect of EMEND on the plasma AUC of R(+) or S(-) warfarin determined on Day 3; however, there was a 34 % decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14 % decrease in INR 5 days after completion of treatment with EMEND.

Tolbutamide
EMEND, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23 % on Day 4, 28 % on Day 8, and 15 % on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15.

Hormonal contraceptives
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of EMEND. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMEND and for 2 months following the last dose of EMEND.

In a clinical study, single doses of an oral contraceptive containing ethinyl estradiol and norethindrone were administered on Days 1 through 21 with EMEND, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg intravenously on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. During days 9 through 21 in this study, there was as much as a 64 % decrease in ethinyl estradiol trough concentrations and as much as a 60 % decrease in norethindrone trough concentrations.

5-HT_3 antagonists
In clinical interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of other medicinal products on the pharmacokinetics of aprepitant
Concomitant administration of EMEND with active substances that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, and protease inhibitors) should be approached cautiously, as the combination is expected to result several-fold in increased plasma concentrations of aprepitant (see section 4.4).

Concomitant administration of EMEND with active substances that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy of EMEND. Concomitant administration of EMEND with herbal preparations containing St. John's Wort (*Hypericum perforatum*) is not recommended.

Ketoconazole
When a single 125 mg dose of aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold.

Rifampicin
When a single 375 mg dose of aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampicin, a strong CYP3A4 inducer, the AUC of aprepitant decreased 91 % and the mean terminal half-life decreased 68 %.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of EMEND. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMEND and for 2 months following the last dose of EMEND (see sections 4.4 and 4.5).

Pregnancy
For aprepitant no clinical data on exposed pregnancies are available. The potential for reproductive toxicity of aprepitant has not been fully characterised, since exposure levels above the therapeutic exposure in humans at the 125 mg/80 mg dose could not be attained in animal studies. These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential effects on reproduction of alterations in neurokinin regulation are unknown. EMEND should not be used during pregnancy unless clearly necessary.

Breast-feeding
Aprepitant is excreted in the milk of lactating rats. It is not known whether aprepitant is excreted in human milk; therefore, breast-feeding is not recommended during treatment with EMEND.

Fertility
The potential for effects of aprepitant on fertility has not been fully characterised because exposure levels above the therapeutic exposure in humans could not be attained in animal studies. These fertility studies did not indicate direct or indirect harmful effects with respect to mating performance, fertility, embryonic/foetal development, or sperm count and motility (see section 5.3).

4.7 Effects on ability to drive and use machines

EMEND may have minor influence on the ability to ride a bicycle and use machines. Dizziness and fatigue may occur following administration of EMEND (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The safety profile of aprepitant was evaluated in approximately 6,500 adults in more than 50 studies and 184 children and adolescents in 2 pivotal paediatric clinical trials.

The most common adverse reactions reported at a greater incidence in adults treated with the aprepitant regimen than with standard therapy in patients receiving Highly Emetogenic Chemotherapy (HEC) were: hiccups (4.6 % versus 2.9 %), alanine aminotransferase (ALT) increased (2.8 % versus 1.1 %), dyspepsia (2.6 % versus 2.0 %), constipation (2.4 % versus 2.0 %), headache (2.0 % versus 1.8 %), and decreased appetite (2.0 % versus 0.5 %). The most common adverse reaction reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy in adults receiving Moderately Emetogenic Chemotherapy (MEC) was fatigue (1.4 % versus 0.9 %).

The most common adverse reactions reported at a greater incidence in paediatric patients treated with the aprepitant regimen than with the control regimen while receiving emetogenic cancer chemotherapy were hiccups (3.3 % versus 0.0 %) and flushing (1.1 % versus 0.0 %).

Tabulated list of adverse reactions
The following adverse reactions were observed in a pooled analysis of the HEC and MEC studies at a greater incidence with aprepitant than with standard therapy or in post-marketing use. The frequency categories given in the table are based on the studies in adults; the observed frequencies in the paediatric studies were similar or lower, unless shown in the table. Some less common ADRs in the adult population were not observed in the paediatric studies.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	Adverse reaction	Frequency
Infection and infestations	candidiasis, staphylococcal infection	rare
Blood and lymphatic system disorders	febrile neutropenia, anaemia	uncommon
Immune system disorders	hypersensitivity reactions including anaphylactic reactions	not known
Metabolism and nutrition disorders	decreased appetite	common
	polydipsia	rare
Psychiatric disorders	anxiety	uncommon
	disorientation, euphoric mood	rare
Nervous system disorders	headache	common
	dizziness, somnolence	uncommon
	cognitive disorder, lethargy, dysgeusia	rare
Eye disorders	conjunctivitis	rare
Ear and labyrinth disorders	tinnitus	rare
Cardiac disorders	palpitations	uncommon
	bradycardia, cardiovascular disorder	rare
Vascular disorders	hot flush/flushing	uncommon
Respiratory, thoracic and mediastinal disorders	hiccups	common
	oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation	rare
Gastrointestinal disorders	constipation, dyspepsia	common
	eructation, nausea[†], vomiting[†], gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence	uncommon
	duodenal ulcer perforation, stomatitis, abdominal distension, faeces hard, neutropenic colitis	rare
Skin and subcutaneous tissue disorders	rash, acne	uncommon
	photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/toxic epidermal necrolysis	rare
	pruritus, urticaria	not known
Musculoskeletal and connective tissue disorders	muscular weakness, muscle spasms	rare

System organ class	Adverse reaction	Frequency
Renal and urinary disorders	dysuria	uncommon
	pollakiuria	rare
General disorders and administration site conditions	fatigue	common
	asthenia, malaise	uncommon
	oedema, chest discomfort, gait disturbance	rare
Investigations	ALT increased	common
	AST increased, blood alkaline phosphatase increased	uncommon
	red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present, urine output increased	rare

†Nausea and vomiting were efficacy parameters in the first 5 days of post-chemotherapy treatment and were reported as adverse reactions only thereafter.

Description of selected adverse reactions
The adverse reactions profiles in adults in the Multiple-Cycle extension of HEC and MEC studies for up to 6 additional cycles of chemotherapy were generally similar to those observed in Cycle 1.

In an additional active-controlled clinical study in 1,169 patients receiving aprepitant and HEC, the adverse reactions profile was generally similar to that seen in the other HEC studies with aprepitant.

Non-CINV studies
Additional adverse reactions were observed in adult patients treated with a single 40 mg dose of aprepitant for postoperative nausea and vomiting (PONV) with a greater incidence than with ondansetron: abdominal pain upper, bowel sounds abnormal, constipation*, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, sub-ileus*, visual acuity reduced, wheezing.
*Reported in patients taking a higher dose of aprepitant.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, emesis induced by a medicinal product may not be effective.

Aprepitant cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, ATC code: A04AD12

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK_1) receptors.

3-day regimen of aprepitant in adults
In 2 randomised, double-blind studies encompassing a total of 1,094 adult patients receiving chemotherapy that included cisplatin ≥ 70 mg/m^2, aprepitant in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with a standard regimen (placebo plus ondansetron 32 mg intravenously administered on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4). Although a 32 mg intravenous dose of ondansetron was used in clinical trials, this is no longer the recommended dose. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information.

Efficacy was based on evaluation of the following composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) primarily during Cycle 1. The results were evaluated for each individual study and for the 2 studies combined.

A summary of the key study results from the combined analysis is shown in Table 1.

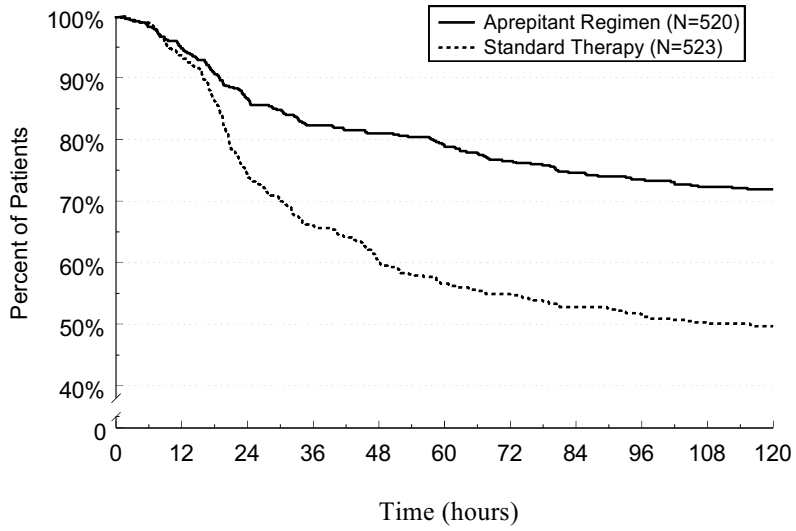
Table 1
Percent of adult patients receiving Highly Emetogenic Chemotherapy responding by treatment group and phase — Cycle 1

COMPOSITE MEASURES	Aprepitant regimen (N= 521)† %	Standard therapy (N= 524)† %	Differences* %	(95 % CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	67.7	47.8	19.9	(14.0, 25.8)
0-24 hours	86.0	73.2	12.7	(7.9, 17.6)
25-120 hours	71.5	51.2	20.3	(14.5, 26.1)
INDIVIDUAL MEASURES				
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	71.9	49.7	22.2	(16.4, 28.0)
0-24 hours	86.8	74.0	12.7	(8.0, 17.5)
25-120 hours	76.2	53.5	22.6	(17.0, 28.2)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	72.1	64.9	7.2	(1.6, 12.8)
25-120 hours	74.0	66.9	7.1	(1.5, 12.6)

* The confidence intervals were calculated with no adjustment for gender and concomitant chemotherapy, which were included in the primary analysis of odds ratios and logistic models.
† One patient in the aprepitant regimen only had data in the acute phase and was excluded from the overall and delayed phase analyses; one patient in the Standard regimen only had data in the delayed phase and was excluded from the overall and acute phase analyses.

The estimated time to first emesis in the combined analysis is depicted by the Kaplan-Meier plot in Figure 1.

Figure 1
Percent of adult patients receiving Highly Emetogenic Chemotherapy
who remain emesis free over time – Cycle 1



Statistically significant differences in efficacy were also observed in each of the 2 individual studies.

In the same 2 clinical studies, 851 adult patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was apparently maintained during all cycles.

In a randomised, double-blind study in a total of 866 adult patients (864 females, 2 males) receiving chemotherapy that included cyclophosphamide 750-1,500 mg/m^2; or cyclophosphamide 500-1,500 mg/m^2 and doxorubicin ($\leq$ 60 mg/m^2) or epirubicin ($\leq$ 100 mg/m^2), aprepitant in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with standard therapy (placebo plus ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1).

Efficacy was based on evaluation of the composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) primarily during Cycle 1.

A summary of the key study results is shown in Table 2.

Table 2
Percent of adult patients responding by treatment group and phase — Cycle 1
Moderately Emetogenic Chemotherapy

COMPOSITE MEASURES	Aprepitant regimen (N= 433)† %	Standard therapy (N= 424) %	Differences* %	(95 % CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	50.8	42.5	8.3	(1.6, 15.0)
0-24 hours	75.7	69.0	6.7	(0.7, 12.7)
25-120 hours	55.4	49.1	6.3	(-0.4, 13.0)
INDIVIDUAL MEASURES				
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	75.7	58.7	17.0	(10.8, 23.2)
0-24 hours	87.5	77.3	10.2	(5.1, 15.3)
25-120 hours	80.8	69.1	11.7	(5.9, 17.5)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	60.9	55.7	5.3	(-1.3, 11.9)
0-24 hours	79.5	78.3	1.3	(-4.2, 6.8)
25-120 hours	65.3	61.5	3.9	(-2.6, 10.3)

* The confidence intervals were calculated with no adjustment for age category (< 55 years, ≥ 55 years) and investigator group, which were included in the primary analysis of odds ratios and logistic models.
† One patient in the aprepitant regimen only had data in the acute phase and was excluded from the overall and delayed phase analyses.

In the same clinical study, 744 adult patients continued into the Multiple-Cycle extension for up to 3 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was apparently maintained during all cycles.

In a second multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 adult patients (652 females, 196 males) receiving a chemotherapy regimen that included any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide intravenously (< 1,500 mg/m^2); or cytarabine intravenously (> 1 g/m^2). Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumour types including 52 % with breast cancer, 21 % with gastrointestinal cancers including colorectal cancer, 13 % with lung cancer and 6 % with gynaecological cancers. The aprepitant regimen in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with standard therapy (placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1).

Efficacy was based on the evaluation of the following primary and key secondary endpoints: No vomiting in the overall period (0 to 120 hours post-chemotherapy), evaluation of safety and tolerability of the aprepitant regimen for chemotherapy induced nausea and vomiting (CINV), and complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy). Additionally, no significant nausea in the overall period (0 to 120 hours post-chemotherapy) was evaluated as an exploratory endpoint, and in the acute and delayed phases as a post-hoc analysis.

A summary of the key study results is shown in Table 3.

Table 3
Percent of adult patients responding by treatment group and phase for Study 2 – Cycle 1
Moderately Emetogenic Chemotherapy

	Aprepitant regimen (N= 425) %	Standard therapy (N= 406) %	Differences* %	(95 % CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	68.7	56.3	12.4	(5.9, 18.9)
0-24 hours	89.2	80.3	8.9	(4.0, 13.8)
25-120 hours	70.8	60.9	9.9	(3.5, 16.3)
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	76.2	62.1	14.1	(7.9, 20.3)
0-24 hours	92.0	83.7	8.3	(3.9, 12.7)
25-120 hours	77.9	66.8	11.1	(5.1, 17.1)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	73.6	66.4	7.2	(1.0, 13.4)
0-24 hours	90.9	86.3	4.6	(0.2, 9.0)
25-120 hours	74.9	69.5	5.4	(-0.7, 11.5)

* The confidence intervals were calculated with no adjustment for gender and region, which were included in the primary analysis using logistic models.

The benefit of aprepitant combination therapy in the full study population was mainly driven by the results observed in patients with poor control with the standard regimen such as in women, even though the results were numerically better regardless of age, tumour type or gender. Complete response to the aprepitant regimen and standard therapy, respectively, was reached in 209/324 (65 %) and 161/320 (50 %) in women and 83/101 (82 %) and 68/87 (78 %) of men.

Paediatric population

In a randomised, double-blind, active comparator-controlled clinical study that included 302 children and adolescents (aged 6 months to 17 years) receiving moderately or highly emetogenic chemotherapy, the aprepitant regimen was compared to a control regimen for the prevention of CINV. The efficacy of the aprepitant regimen was evaluated in a single cycle (Cycle 1). Patients had the opportunity to receive open-label aprepitant in subsequent cycles (Optional Cycles 2-6); however efficacy was not assessed in these optional cycles. The aprepitant regimen for adolescents aged 12 through 17 years (n=47) consisted of EMEND capsules 125 mg orally on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron on Day 1. The aprepitant regimen for children aged 6 months to less than 12 years (n=105) consisted of EMEND powder for oral suspension 3.0 mg/kg (up to 125 mg) orally on Day 1 and 2.0 mg/kg (up to 80 mg) orally on Days 2 and 3 in combination with ondansetron on Day 1. The control regimen in adolescents aged 12 through 17 years (n=48) and children aged 6 months to less than 12 years (n=102) consisted of placebo for aprepitant on Days 1, 2 and 3 in combination with ondansetron on Day 1. EMEND or placebo and ondansetron were administered 1 hour and 30 minutes prior to initiation of chemotherapy, respectively. Intravenous dexamethasone was permitted as part of the antiemetic regimen for paediatric patients in both age groups, at the discretion of the physician. A dose reduction (50 %) of dexamethasone was required for paediatric patients receiving aprepitant. No dose reduction was required for paediatric patients receiving the control regimen. Of the paediatric patients, 29 % in the aprepitant regimen and 28 % in the control regimen used dexamethasone as part of the regimen in Cycle 1.

The antiemetic activity of EMEND was evaluated over a 5-day (120 hour) period following the initiation of chemotherapy on Day 1. The primary endpoint was complete response in the delayed phase (25 to 120 hours following initiation of chemotherapy) in Cycle 1. A summary of the key study results are shown in Table 4.

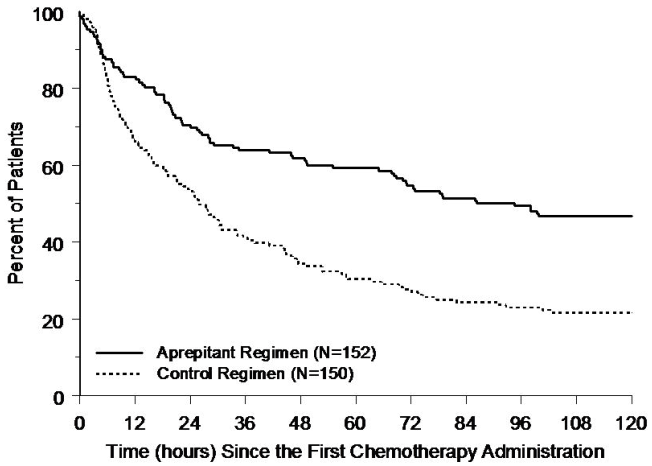
Table 4
Number (%) of paediatric patients with complete response and no vomiting by treatment group and phase – Cycle 1 (Intent to treat population)

	Aprepitant regimen n/m (%)	Control regimen n/m (%)
PRIMARY ENDPOINT		
Complete response* – Delayed phase	77/152 (50.7)†	39/150 (26.0)
OTHER PRESPECIFIED ENDPOINTS		
Complete response* – Acute phase	101/152 (66.4)‡	78/150 (52.0)
Complete response* – Overall phase	61/152 (40.1)†	30/150 (20.0)
No vomiting§ – Overall phase	71/152 (46.7)†	32/150 (21.3)

*Complete response = No vomiting or retching or dry heaves and no use of rescue medication.
†$p < 0.01$ when compared to control regimen.
‡$p < 0.05$ when compared to control regimen.
§No vomiting = No vomiting or retching or dry heaves.
n/m = Number of patients with desired response/number of patients included in time point.
Acute phase: 0 to 24 hours following initiation of chemotherapy.
Delayed phase: 25 to 120 hours following initiation of chemotherapy.
Overall phase: 0 to 120 hours following initiation of chemotherapy.

The estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen (estimated median time to first vomiting was 94.5 hours) compared with the control regimen group (estimated median time to first vomiting was 26.0 hours) as depicted in the Kaplan-Meier curves in Figure 2.

Figure 2
Time to first vomiting episode from start of chemotherapy administration - paediatric patients in the overall phase-Cycle 1 (Intent to treat population)



An analysis of efficacy in subpopulations in Cycle 1 demonstrated that, regardless of age category, gender, use of dexamethasone for antiemetic prophylaxis, and emetogenicity of chemotherapy, the aprepitant regimen provided better control than the control regimen with respect to the complete response endpoints.

5.2 Pharmacokinetic properties

Aprepitant displays non-linear pharmacokinetics. Both clearance and absolute bioavailability decrease with increasing dose.

Absorption
The mean absolute oral bioavailability of aprepitant is 67 % for the 80 mg capsule and 59 % for the 125 mg capsule. The mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (t_{max}). Oral administration of the capsule with an approximately 800 Kcal standard breakfast resulted in an up to 40 % increase in AUC of aprepitant. This increase is not considered clinically relevant.

The pharmacokinetics of aprepitant is non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26 % greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state.

Following oral administration of a single 125 mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} (mean±SD) was 19.6 ± 2.5 µg•h/mL and 21.2 ± 6.3 µg•h/mL on Days 1 and 3, respectively. C_{max} was 1.6 ± 0.36 µg/mL and 1.4 ± 0.22 µg/mL on Days 1 and 3, respectively.

Distribution
Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 66 L in humans.

Biotransformation
Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 19 % of the radioactivity in plasma over 72 hours following a single intravenous administration 100 mg dose of [^{14}C]-fosaprepitant, a prodrug for aprepitant, indicating a substantial presence of metabolites in the plasma. Twelve metabolites of aprepitant have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains and the resultant metabolites were only weakly active. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 and potentially with minor contribution by CYP1A2 and CYP2C19.

Elimination
Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. Following a single intravenously administered 100 mg dose of [^{14}C]-fosaprepitant, a prodrug for aprepitant, to healthy subjects, 57 % of the radioactivity was recovered in urine and 45 % in faeces.

The plasma clearance of aprepitant is dose-dependent, decreasing with increased dose and ranged from approximately 60 to 72 mL/min in the therapeutic dose range. The terminal half-life ranged from approximately 9 to 13 hours.

Pharmacokinetics in special populations
Gender: Following oral administration of a single 125 mg dose of aprepitant, the C_{max} for aprepitant is 16 % higher in females as compared with males. The half-life of aprepitant is 25 % lower in females as compared with males and its t_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dose adjustment for EMEND is necessary based on gender.

Hepatic impairment: Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a clinically relevant extent. No dose adjustment is necessary for patients with mild hepatic impairment. Conclusions regarding the influence of moderate hepatic impairment (Child-Pugh class B) on aprepitant pharmacokinetics cannot be drawn from available data. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment: A single 240 mg dose of aprepitant was administered to patients with severe renal impairment (CrCl < 30 mL/min) and to patients with end stage renal disease (ESRD) requiring haemodialysis.

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21 % and C_{max} decreased by 32 %, relative to healthy subjects. In patients with ESRD undergoing haemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42 % and C_{max} decreased by 32 %. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound aprepitant was not significantly affected in patients with renal impairment compared with healthy subjects. Haemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2 % of the dose was recovered in the dialysate.

No dose adjustment for EMEND is necessary for patients with renal impairment or for patients with ESRD undergoing haemodialysis.

Paediatric population: As part of a 3-day regimen, dosing of aprepitant capsules (125/80/80-mg) in adolescent patients (aged 12 through 17 years) achieved an AUC_{0-24hr} above 17 µg•hr/mL on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.4 µg/mL in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.3 µg/mL on Day 1, occurring at approximately 4 hours. As part of a 3-day regimen, dosing of aprepitant powder for oral suspension (3/2/2-mg/kg) in patients aged 6 months to less than 12 years achieved an AUC_{0-24hr} above 17 µg•hr/mL on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.1 µg/mL in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.2 µg/mL on Day 1, occurring between 5 and 7 hours.

A population pharmacokinetic analysis of aprepitant in paediatric patients (aged 6 months through 17 years) suggests that gender and race have no clinically meaningful effect on the pharmacokinetics of aprepitant.

Relationship between concentration and effect

Using a highly specific NK_1-receptor tracer, positron emission tomography (PET) studies in healthy young men have shown that aprepitant penetrates into the brain and occupies NK_1 receptors in a dose- and plasma-concentration-dependent manner. Aprepitant plasma concentrations achieved with the 3-day regimen of EMEND in adults are predicted to provide greater than 95 % occupancy of brain NK_1 receptors.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. However, it should be noted that systemic exposure in rodents was similar or even lower than therapeutic exposure in humans at the 125 mg/80 mg dose. In particular, although no adverse effects were noted in reproduction studies at human exposure levels, the animal exposures are not sufficient to make an adequate risk assessment in man.

In a juvenile toxicity study in rats treated from postnatal day 10 to day 63 aprepitant led to an earlier vaginal opening in females from 250 mg/kg b.i.d. and to a delayed preputial separation in males, from 10 mg/kg b.i.d. There were no margins to clinically relevant exposure. There were no treatment-related effects on mating, fertility or embryonic/foetal survival, and no pathological changes in the reproductive organs. In a juvenile toxicity study in dogs treated from postnatal day 14 to day 42, a decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and oedema of vaginal tissues were seen in females from 4 mg/kg/day. There were no margins to clinically relevant exposure of aprepitant. For short term treatment according to recommended dose regimen these findings are considered unlikely to be clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose (E 463)
Sodium laurilsulfate
Sucrose
Lactose (anhydrous)
Red iron oxide (E 172)
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Unopened sachet: 2 years
After reconstitution: The oral suspension can be kept at room temperature (not above 30°C) for up to 3 hours. It can also be stored refrigerated (between 2°C and 8°C) for up to 72 hours.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

PET/aluminium/LLDPE sachets
Single-use carton
Each carton contains one sachet with the powder for oral suspension, one 1 mL and one 5 mL oral dispenser (polypropylene with silicone o-ring), one cap, and one mixing cup (polypropylene).

6.6 Special precautions for disposal and other handling

The content of each single-use sachet is to be suspended in 4.6 mL of water giving a final concentration of 25 mg per mL.

- For more details on preparation and administration of the suspension, see the package leaflet and the instructions for preparation of the oral suspension for healthcare professionals.
- Use the 5 mL oral dispenser to measure 4.6 mL of water, which is added into the mixing cup.
- Pour entire contents of the sachet into the 4.6 mL of water and mix.
- Once mixed, measure the recommended volume (dose) of suspension with the oral dispenser. Choose the oral dispenser based on the dose. Use the 1 mL oral dispenser if the dose is 1 mL or less and use the 5 mL oral dispenser if the dose is more than 1 mL. Administer the dose orally. If the dose is not administered immediately after measuring, the filled oral dispenser can be refrigerated (between 2°C and 8°C) for up to 72 hours prior to use.
- The oral suspension can be kept at room temperature (not above 30°C) for up to 3 hours, prior to administration.
- Discard any remaining suspension and waste material.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/03/262/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 11 November 2003
Date of latest renewal: 22 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B. V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING – STANDARD PACK (CARTON)

1. NAME OF THE MEDICINAL PRODUCT

EMEND 80 mg hard capsules
aprepitant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 80 mg of aprepitant.

3. LIST OF EXCIPIENTS

Contains sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 hard capsule
2-day treatment pack containing: 2 x 80 mg hard capsule
5 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/262/001 1 hard capsule
EU/1/03/262/002 2 x 1 hard capsule
EU/1/03/262/003 5 x 1 hard capsule

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EMEND 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING (INCLUDING 2 HARD CAPSULES 80 MG)

IMMEDIATE PACKAGING – TRIFOLD – 2-day treatment pack

1. NAME OF THE MEDICINAL PRODUCT

EMEND 80 mg hard capsules
aprepitant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 80 mg of aprepitant.

3. LIST OF EXCIPIENTS

Contains sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2-day treatment pack containing:
2 x 80 mg hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Please read enclosed leaflet before use.

See enclosed leaflet for additional information about how to take EMEND.

WHEN and HOW to take EMEND

Your doctor has prescribed EMEND, an anti-emetic, to help prevent nausea and vomiting associated with chemotherapy.

HOW:
EMEND 80 mg hard capsules are taken just once a day for 2 consecutive days.
EMEND capsules can be taken with or without food.

Do not remove all capsules at one time.

To remove, push capsules through from this side.

Start of Therapy
WHEN:
Take one EMEND 80 mg capsule each morning. Start on the day after your chemotherapy.

Day 1

Day 2

EMEND 80 mg capsule

As nausea and vomiting may occur in the days following your chemotherapy, it is important that you take EMEND for 2 consecutive days as prescribed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/262/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

EMEND 80 mg hard capsules
aprepitant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING – STANDARD PACK (CARTON)

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg hard capsules
aprepitant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 125 mg of aprepitant.

3. LIST OF EXCIPIENTS

Contains sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 hard capsule
5 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/262/004 1 hard capsule
EU/1/03/262/005 5 x 1 hard capsule

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EMEND 125 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg hard capsules
aprepitant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING – TRIFOLD PACK (CARTON) – 3-day treatment pack

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg hard capsule
EMEND 80 mg hard capsules
aprepitant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 125 mg hard capsule contains 125 mg of aprepitant.
Each 80 mg hard capsule contains 80 mg of aprepitant.

3. LIST OF EXCIPIENTS

Contains sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

3-day treatment pack containing:
1 x 125 mg hard capsule and
2 x 80 mg hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/262/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EMEND 125 mg/80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING (INCLUDING 1 HARD CAPSULE 125 MG AND 2 HARD CAPUSULES 80 MG)

IMMEDIATE PACKAGING – TRIFOLD – 3-day treatment pack

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg hard capsule
EMEND 80 mg hard capsules
aprepitant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 125 mg hard capsule contains 125 mg of aprepitant.
Each 80 mg hard capsule contains 80 mg of aprepitant.

3. LIST OF EXCIPIENTS

Contains sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

3-day treatment pack containing:
1 x 125 mg hard capsule and
2 x 80 mg hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Please read enclosed leaflet before use.

See enclosed leaflet for additional information about how to take EMEND.

WHEN and HOW to take EMEND

Your doctor has prescribed EMEND, an anti-emetic, to help prevent nausea and vomiting associated with chemotherapy.

HOW:
EMEND is taken just once a day for 3 consecutive days.
EMEND capsules can be taken with or without food.

Do not remove all capsules at one time.

To remove, push capsules through from this side.

Start of Therapy
WHEN:
Take one EMEND 125 mg capsule by mouth 1-hour BEFORE you start your chemotherapy treatment.

Day 1

EMEND 125 mg capsule

WHEN:
Take one EMEND 80 mg capsule each morning on the next two days.

Day 2

Day 3

EMEND 80 mg capsule

As nausea and vomiting may occur in the days following your chemotherapy, it is important that you take EMEND for 3 consecutive days as prescribed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/262/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON EMEND 125 mg powder for oral suspension

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg powder for oral suspension
aprepitant
For children aged 6 months to less than 12 years

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains125 mg of aprepitant. After reconstitution, 1 mL of oral suspension contains 25 mg of aprepitant.

3. LIST OF EXCIPIENTS

Contains sucrose and lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
One sachet, two oral dispensers, one cap and one mixing cup.

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/262/011

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EMEND 125 mg powder for oral suspension

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE SMALL IMMEDIATE PACKAGING

Sachet for EMEND 125 mg powder for oral suspension

1. NAME OF THE MEDICINAL PRODUCT

EMEND 125 mg powder for oral suspension
aprepitant
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

EMEND 125 mg hard capsules
EMEND 80 mg hard capsules
aprepitant

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. If you are the parent of a child taking EMEND, please read this information carefully.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor, pharmacist, or nurse.
- This medicine has been prescribed for you or the child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same.
- If you or the child gets any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EMEND is and what it is used for

EMEND contains the active substance aprepitant and belongs to a group of medicines called "neurokinin 1 (NK_1) receptor antagonists". The brain has a specific area that controls nausea and vomiting. EMEND works by blocking signals to that area, thereby reducing nausea and vomiting. EMEND capsules are used in adults and adolescents from the age of 12 years **in combination with other medicines** to prevent nausea and vomiting caused by chemotherapy (cancer treatment) that are strong and moderate triggers of nausea and vomiting (such as cisplatin, cyclophosphamide, doxorubicin or epirubicin).

2. What you need to know before you take or give EMEND

Do not take EMEND
- if you or the child is allergic to aprepitant or any of the other ingredients of this medicine (listed in section 6).
- with medicines containing pimozide (used to treat psychiatric illnesses), terfenadine and astemizole (used for hay fever and other allergic conditions), cisapride (used for treating digestive problems). Tell the doctor if you or the child is taking these medicines since the treatment must be modified before you or the child start taking EMEND.

Warnings and precautions
Talk to the doctor, pharmacist, or nurse before you take EMEND or give this medicine to the child.

Before treatment with EMEND, tell the doctor if you or the child have liver disease because the liver is important in breaking down the medicine in the body. The doctor may therefore have to monitor the condition of your or the child's liver.

Children and adolescents
Do not give EMEND 80 mg and 125 mg capsules to children under 12 years of age, because the 80 mg and 125 mg capsules have not been studied in this population.

Other medicines and EMEND
EMEND can affect other medicines both during and after treatment with EMEND. There are some medicines that should not be taken with EMEND (such as pimozide, terfenadine, astemizole, and cisapride) or that require a dose adjustment (see also 'Do not take EMEND').

The effects of EMEND or other medicines might be influenced if you or the child take EMEND together with other medicines including those listed below. Please talk to the doctor or pharmacist if you or the child is taking any of the following medicines:

- birth control medicines which can include birth control pills, skin patches, implants, and certain Intrauterine devices (IUDs) that release hormones may not work adequately when taken together with EMEND. Another or additional non-hormonal form of birth control should be used during treatment with EMEND and for up to 2 months after using EMEND,
- cyclosporine, tacrolimus, sirolimus, everolimus (immunosuppressants),
- alfentanil, fentanyl (used to treat pain),
- quinidine (used to treat an irregular heart beat),
- irinotecan, etoposide, vinorelbine, ifosfamide (medicines used to treat cancer),
- medicines containing ergot alkaloid derivatives such as ergotamine and diergotamine (used for treating migraines),
- warfarin, acenocoumarol (blood thinners; blood tests may be required),
- rifampicin, clarithromycin, telithromycin (antibiotics used to treat infections),
- phenytoin (a medicine used to treat seizures),
- carbamazepine (used to treat depression and epilepsy),
- midazolam, triazolam, phenobarbital (medicines used to produce calmness or help you sleep),
- St. John's Wort (an herbal preparation used to treat depression),
- protease inhibitors (used to treat HIV infections),
- ketoconazole except shampoo (used to treat Cushing's syndrome - when the body produces an excess of cortisol),
- itraconazole, voriconazole, posaconazole (antifungals),
- nefazodone (used to treat depression),
- corticosteroids (such as dexamethasone and methylprednisolone),
- anti-anxiety medicines (such as alprazolam),
- tolbutamide (a medicine used to treat diabetes).

Tell the doctor or pharmacist if you or the child are taking, have recently taken, or might take any other medicines.

Pregnancy and breast-feeding
This medicine should not be used during pregnancy unless clearly necessary. If you or the child are pregnant or breast-feeding, may be pregnant or are planning to have a baby, ask the doctor for advice before taking this medicine.

For information regarding birth control, see 'Other medicines and EMEND'.

It is not known whether EMEND is excreted in human milk; therefore, breast-feeding is not recommended during treatment with this medicine. It is important to tell the doctor if you or the child are breast-feeding or are planning to breast-feed before taking this medicine.

Driving and using machines
It should be taken into account that some people feel dizzy and sleepy after taking EMEND. If you or the child feels dizzy or sleepy, avoid driving, riding a bicycle or using machines or tools after taking this medicine (see 'Possible side effects').

EMEND contains sucrose
EMEND capsules contain sucrose. If you or the child have been told by your doctor that you or the child have an intolerance to some sugars, contact the doctor before taking this medicine.

EMEND contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to take EMEND

Always take this medicine or give this medicine to the child exactly as the doctor, pharmacist or nurse has told you. You should check with the doctor, pharmacist or nurse if you are not sure. Always take EMEND together with other medicines, to prevent nausea and vomiting. After treatment with EMEND, the doctor may ask you or the child to continue taking other medicines including a corticosteroid (such as dexamethasone) and a '5-HT_3 antagonist' (such as ondansetron) for preventing nausea and vomiting. Check with the doctor, pharmacist or nurse if you are not sure.

The recommended oral dose of EMEND is:
Day 1:
- one 125 mg capsule 1 hour before you start your chemotherapy session

and

Days 2 and 3:
- one 80 mg capsule each day
- If no chemotherapy is given, take EMEND in the morning.
- If chemotherapy is given, take EMEND 1 hour before you start your chemotherapy session.

EMEND can be taken with or without food.

Swallow the capsule whole with some liquid.

If you take more EMEND than you should
Do not take more capsules than the doctor recommends. If you or the child has taken too many capsules, contact your doctor immediately.

If you forget to take EMEND
If you or the child has missed a dose, contact your doctor for advice.

If you have any further questions on the use of this medicine, ask the doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking EMEND and see a doctor immediately if you or the child notice any of the following side effects, which may be serious, and for which you or the child may need urgent medical treatment:
- Hives, rash, itching, difficulty breathing or swallowing (frequency not known, cannot be estimated from the available data); these are signs of an allergic reaction.

Other side effects that have been reported are listed below.

Common side effects (may affect up to 1 in 10 people) are:
- constipation, indigestion,
- headache,
- tiredness,
- loss of appetite,
- hiccups,

- increased amount of liver enzymes in your blood.

Uncommon side effects (may affect up to 1 in 100 people) are:
- dizziness, sleepiness,
- acne, rash,
- anxiousness,
- burping, nausea, vomiting, heartburn, stomach pain, dry mouth, passing wind,
- increased painful or burning urination,
- weakness, generally feeling unwell,
- hot flush/reddening of the face or skin,
- fast or irregular heartbeats,
- fever with increased risk of infection, lowering of red blood cells.

Rare side effects (may affect up to1 in 1 000 people) are:
- difficulty thinking, lack of energy, taste disturbance,
- sensitivity of the skin to sun, excessive sweating, oily skin, sores on skin, itching rash, Stevens-Johnson syndrome/toxic epidermal necrolysis (rare severe skin reaction),
- euphoria (feeling of extreme happiness), disorientation,
- bacterial infection, fungal infection,
- severe constipation, stomach ulcer, inflammation of the small intestine and colon, sores in mouth, bloating,
- frequent urination, passing more urine than normal, presence of sugar or blood in urine,
- chest discomfort, swelling, change in the manner of walking,
- cough, mucus in back of throat, throat irritation, sneezing, sore throat,
- eye discharge and itching,
- ringing in the ear,
- muscle spasms, muscle weakness,
- excessive thirst,
- slow heartbeat, heart and blood vessel disease,
- lowering of white blood cells, low sodium levels in the blood, weight loss.

Reporting of side effects
If you or the child gets any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EMEND

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

Do not remove the capsule from its blister until you are ready to take it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EMEND contains
- The active substance is aprepitant. Each 125 mg hard capsule contains 125 mg of aprepitant. Each 80 mg hard capsule contains 80 mg of aprepitant.
- The other ingredients are sucrose, microcrystalline cellulose (E 460), hydroxypropylcellulose (E 463), sodium laurilsulfate, gelatin, titanium dioxide (E 171), shellac, potassium hydroxide, and black iron oxide (E 172); the 125 mg hard capsule also contains red iron oxide (E 172) and yellow iron oxide (E 172).

What EMEND looks like and contents of the pack
The 125 mg hard capsule is opaque with a white body and pink cap with “462” and “125 mg” printed radially in black ink on the body.
The 80 mg hard capsule is opaque with a white cap and body with “461” and “80 mg” printed radially in black ink on the body.

EMEND 125 mg and 80 mg hard capsules are supplied in the following pack sizes:
- Aluminium blister containing one 80 mg capsule
- 2-day treatment pack containing two 80 mg capsules
- 5 Aluminium blisters each containing one 80 mg capsule
- Aluminium blister containing one 125 mg capsule
- 5 Aluminium blisters each containing one 125 mg capsule
- 3-day treatment pack containing one 125 mg capsule and two 80 mg capsules

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the user

EMEND 125 mg powder for oral suspension
aprepitant

Read all of this leaflet carefully before you start using this medicine because it contains important information. This leaflet has been written for the parent or carer who will give this medicine to the child - please read this information carefully.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor, pharmacist, or nurse.
- This medicine has been prescribed for the child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same.
- If the child gets any side effects, talk to the doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EMEND is and what it is used for

EMEND contains the active substance 'aprepitant.' It belongs to a group of medicines called 'neurokinin 1 (NK_1) receptor antagonists'. The brain has a specific area that controls nausea and vomiting. EMEND works by blocking signals to that area, thereby reducing nausea and vomiting. The powder for oral suspension is used in children aged 6 months to less than 12 years **in combination with other medicines** to prevent nausea and vomiting caused by chemotherapy (cancer treatment) that are strong and moderate triggers of nausea and vomiting (such as cisplatin, cyclophosphamide, doxorubicin or epirubicin).

2. What you need to know before you give EMEND

Do not give EMEND
- if the child is allergic to aprepitant or any of the other ingredients of this medicine (listed in section 6).
- if the child is using medicines that contain 'pimozide' (for mental health problems).
- if the child is using 'terfenadine' or 'astemizole' (for hay fever and other allergies).
- if the child is using 'cisapride' - (for problems with digestion).

Do not give this medicine if any of the above applies to the child and tell the child's doctor if they are using any of the medicines above. This is because their treatment will need to be changed before starting this medicine. If you are not sure, talk to the doctor, pharmacist or nurse before giving this medicine.

Warnings and precautions
Talk to the doctor, pharmacist, or nurse before giving this medicine to the child.

Liver problems
Tell the doctor before treatment with EMEND starts, if the child has liver problems. This is because the liver is important in breaking down the medicine in the body. The doctor may have to check the condition of the child's liver during treatment.

Children and adolescents
Do not give EMEND powder for oral suspension to children under 6 months of age or who weigh less than 6 kg, or to adolescents between 12 and 18 years, because the powder for oral suspension has not been studied in this population.

Other medicines and EMEND
Tell the doctor, pharmacist or nurse if the child is using, has recently used or might use any other medicines. This is because EMEND can affect how other medicines work, during and after treatment with EMEND. Also, some other medicines can affect the way this medicine works.

Do not give EMEND and tell the doctor or pharmacist if the child is using any of the following medicines (see also 'Do not give EMEND'). This is because their treatment will need to be changed before starting EMEND:
- pimozide - for mental health problems,
- terfenadine and astemizole - for hay fever and other allergies,
- cisapride - for problems with digestion.

Do not give this medicine and tell the doctor or pharmacist if any of the above apply to the child.

Talk to the doctor, pharmacist or nurse if the child is taking any of the following medicines:
- medicines that affect the immune system – such as cyclosporine, tacrolimus, sirolimus, everolimus,
- alfentanil, fentanyl – for pain,
- quinidine – for irregular heart beat,
- medicines for cancer – such as irinotecan, etoposide, vinorelbine, ifosfamide,
- medicines containing 'ergot alkaloid derivatives' - such as ergotamine and diergotamine - for migraines,
- medicines that thin the blood – such as warfarin, acenocoumarol. Your child may need blood tests during treatment with EMEND,
- antibiotics to treat infections – such as rifampicin, clarithromycin, telithromycin,
- phenytoin - for fits (seizures),
- carbamazepine - for depression and epilepsy,
- midazolam, triazolam, phenobarbital - to produce calmness or help you sleep,
- St. John's Wort - a herbal medicine for depression,
- protease inhibitors - for HIV infections,
- ketoconazole except shampoo (used to treat Cushing's syndrome - when the body produces an excess of cortisol),
- antifungal medicines such as itraconazole, voriconazole, posaconazole,
- nefazodone - for depression,
- corticosteroids - such as dexamethasone and methylprednisolone,
- medicines for anxiety such as alprazolam,
- tolbutamide - for diabetes,
- contraceptive medicines including pills, patches, implants, and some Intrauterine devices (IUDs) that release hormones. These may not work properly when taken with this medicine. You may need to use a different or an extra non-hormonal contraceptive during treatment with this medicine and for up to 2 months after treatment has finished.

If any of the above apply to the child (or you are not sure), talk to the doctor, pharmacist or nurse before giving this medicine.

Pregnancy and breast-feeding
This medicine should not be used during pregnancy and breast-feeding unless clearly necessary.

For information regarding pregnancy, breast-feeding and contraception, ask your doctor for advice.

Driving and using machines
It should be taken into account that some people may feel dizzy and sleepy after taking EMEND. If the child feels dizzy or sleepy, they should not ride a bicycle or use any tools or machines.

EMEND contains sucrose and lactose
The powder for oral suspension contains sucrose and lactose. If a doctor has told you that the child has an intolerance to some sugars, contact the doctor before giving this medicine to the child.

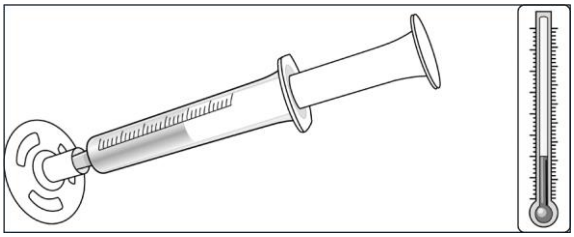
EMEND contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

3. How to give EMEND

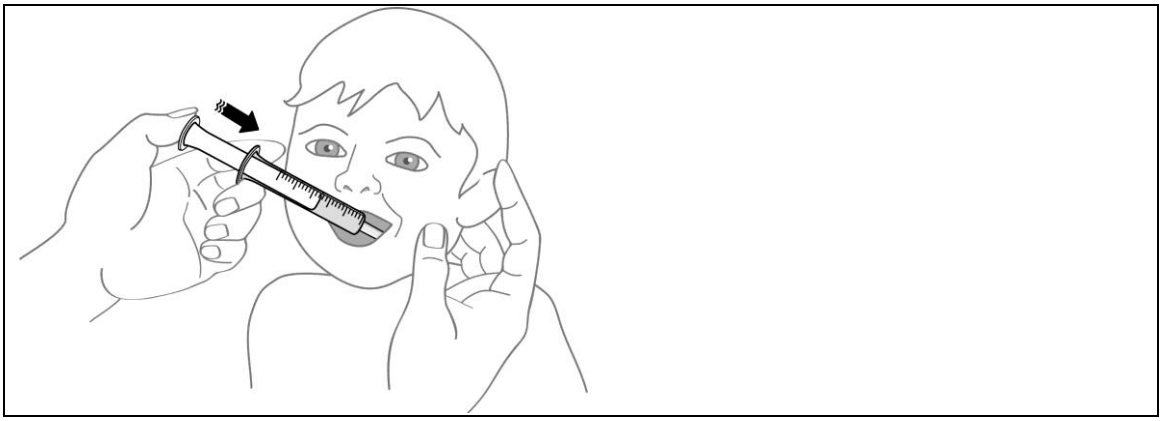
Healthcare professionals: See the instructions for preparation of the oral suspension for healthcare professionals at the end of this package leaflet. This tells you how to prepare a dose of EMEND as an oral suspension.

Parents and caregivers: Always give this medicine to the child exactly as the doctor, pharmacist or nurse has told you. Check with the child's doctor, pharmacist or nurse if you are not sure.
It is very important that this medicine is given exactly as directed below.

For each dose of EMEND, you will get a pre-filled oral dispenser that contains the child's prescribed dose.
Keep the oral dispenser in the refrigerator (between 2 °C and 8 °C) until you give the medicine to the child.



Use this medicine within 2 days of getting the medicine from the healthcare provider.
The medicine can be kept at room temperature (not above 30 °C) for up to 3 hours, prior to administration.



The colour of the medicine in the oral dispenser may be different shades of pink (light pink to dark pink). This is normal and the medicine is okay to use.

- Take the cap off the oral dispenser.
- Place the tip of the oral dispenser in the child's mouth along in the inner cheek on either the right or left side.
- Slowly push the plunger all the way down to give all the medicine in the oral dispenser.

If the child could not take the whole dose, call the child's healthcare provider.

When you have finished do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

How much to give
- The doctor will work out the right dose of powder for oral suspension based on the weight of the child.
- Do not change the dose or stop treatment without first talking to the doctor, pharmacist or nurse.

When to give
Day 1:
- Give this medicine one hour before the start of the chemotherapy session.

Day 2 and Day 3:
- If the child will not have chemotherapy - give this medicine in the morning.
- If the child will have chemotherapy - give this medicine one hour before the start of the chemotherapy session.

EMEND can be given with or without food.

Always give this medicine together with other medicines, to prevent nausea and vomiting. After treatment with EMEND, the doctor may ask the child to continue taking other medicines for preventing nausea and vomiting which may include:
- a corticosteroid - such as dexamethasone and
- a '5-HT_3 antagonist' - such as ondansetron

Check with the doctor, pharmacist or nurse if you are not sure.

If you give more EMEND than you should
Do not give the child more of this medicine than the doctor recommends. If you give the child more than you should, contact the doctor straight away.

If you forget to give EMEND
If the child misses a dose of this medicine, talk to the doctor.
If you have any further questions on the use of this medicine, ask the doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop giving this medicine and see a doctor straight away if you or the child notice any of the following serious side effects – the child may need urgent medical treatment:
- allergic reaction – the signs may include hives, rash, itching, difficulty breathing or swallowing (it is not known how often this happens).

Stop giving this medicine and see a doctor straight away if you notice any of the serious side effects above.

Other side effects
Tell the doctor, pharmacist or nurse if you or the child notice any of the following side effects:

Common: may affect up to 1 in 10 people
- constipation or indigestion,
- headache,
- feeling tired,
- loss of appetite,
- hiccups,

- increased amount of liver enzymes in the blood (shown in tests).

Uncommon: may affect up to 1 in 100 people
- feeling dizzy or sleepy,
- acne, rash,
- feeling anxious,
- burping, nausea, vomiting, heartburn, stomach pain, dry mouth, passing wind,
- pain or burning when urinating,
- feeling weak, generally feeling unwell,
- hot flushes/reddening of the face or skin,
- fast or irregular heart beat,
- fever with increased risk of infection, low number of red blood cells (shown in tests).

Rare: may affect up to 1 in 1 000 people
- difficulty thinking, lack of energy, changes in taste,
- sensitivity of the skin to sun, excessive sweating, oily skin, sores on the skin, itchy rash, Stevens-Johnson syndrome or toxic epidermal necrolysis (rare severe skin reactions),
- euphoria (feeling of extreme happiness), feeling confused,
- bacterial infection, fungal infection,
- severe constipation, stomach ulcer, inflamed small intestine and colon, sores in the mouth, bloating,
- urinating more often or passing more urine than normal, sugar or blood in urine,
- chest discomfort, swelling, change in the manner of walking,
- cough, mucus in the back of the throat, throat irritation, sneezing, sore throat,
- eye discharge and itching,
- ringing in the ears,
- muscle spasms, muscle weakness,
- feeling very thirsty,
- slow heartbeat, heart and blood vessel disease,
- low number of white blood cells, low sodium levels in the blood, weight loss.

Reporting of side effects
If the child gets any side effects, talk to the doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EMEND

Keep this medicine out of the sight and reach of children.

Before reconstitution:

Emend will generally be stored by healthcare professionals. The storage details, should you need them, are as follows:
Do not give this medicine to the child after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

After reconstitution:

The oral suspension can be kept at room temperature (not above 30 °C) for up to 3 hours, prior to administration. It can also be stored refrigerated (between 2 °C and 8 °C) for up to 72 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EMEND contains
- The active substance is aprepitant. Each sachet contains 125 mg of aprepitant. After reconstitution, 1 mL oral suspension contains 25 mg of aprepitant.
- The other ingredients are hydroxypropyl-cellulose (E 463), sodium laurilsulfate, sucrose and lactose (see section 2 under 'EMEND contains sucrose and lactose'), red iron oxide (E 172) and sodium stearyl fumarate.

What EMEND looks like and contents of the pack
The powder for oral suspension is a pink to light pink powder in a single-use sachet.

Single-use carton
Pack size of one carton contains one sachet, one 1 mL and one 5 mL oral dispenser (polypropylene with silicone o-ring), one cap and one mixing cup (polypropylene).

Marketing Authorisation Holder and Manufacturer

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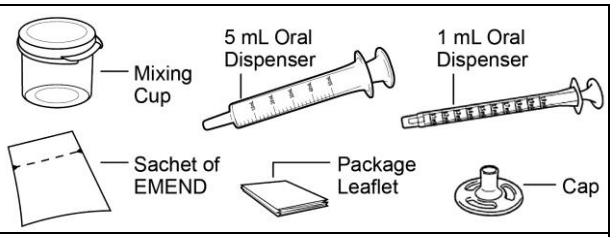
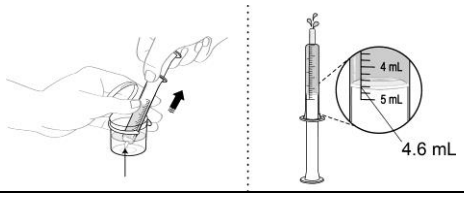
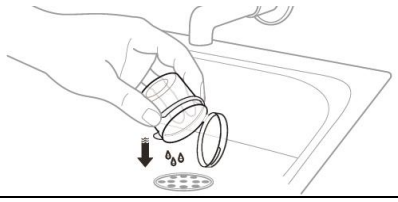
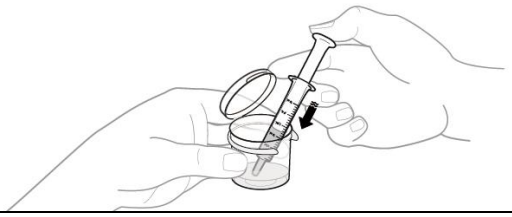
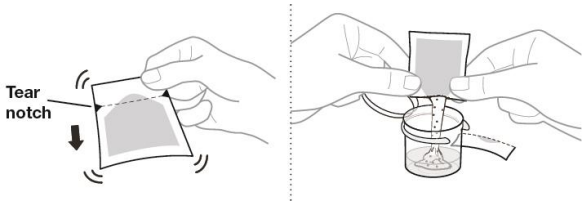
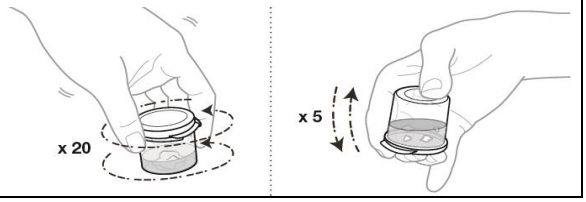
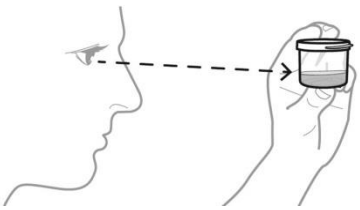
Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Instructions for healthcare professionals on the preparation of the oral suspension

Each pack of EMEND contains a sachet with the powder for oral suspension, a 1 mL and a 5 mL oral dispenser, one cap and one mixing cup.	
1. Fill the mixing cup with room temperature drinking water.	
2. Fill the 5 mL oral dispenser with 4.6 mL of water from the mixing cup. **Make sure no air is in the oral dispenser (if air is present, remove).**	
3. Discard all the unused water remaining in the mixing cup.	
4. Add the 4.6 mL of water from the oral dispenser back into the mixing cup.	
5. Each sachet of EMEND for oral suspension contains 125 mg of aprepitant which is to be suspended in 4.6 mL of water giving a final concentration of 25 mg/mL. Hold the EMEND powder for oral suspension sachet upright and shake the contents to the bottom before opening the sachet. 6. Pour the entire contents of the sachet into the 4.6 mL of water in the mixing cup and snap the lid shut.	
7. Mix the EMEND suspension gently by swirling 20 times; then gently invert the mixing cup 5 times. To prevent foaming, do not shake the mixing cup. The mixture will be cloudy pink to light pink.	

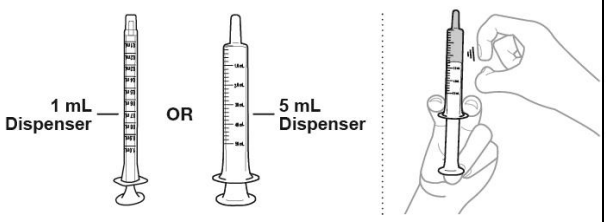
8. Check the EMEND mixture for any clumps or foaming:
   - If any clumps are present, repeat Step 7 until there are no clumps.
   - If there is any foam, wait for the foam to disappear before going on to Step 9.



9. Fill the oral dispenser with the prescribed dose from the mixing cup according to the table below.
   - Choose the oral dispenser based on dose:
     - Use 1 mL oral dispenser if dose is 1 mL or less.
     - Use 5 mL oral dispenser if dose is more than 1 mL.
   - It is common to have medicine leftover in the cup.

Make sure no air is in the oral dispenser (if air is present, remove).

Make sure the oral dispenser contains the prescribed dose.

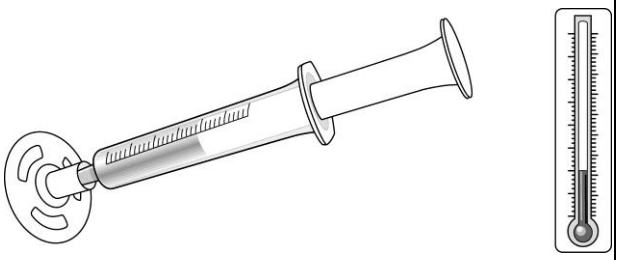


	Day 1	Day 2	Day 3
EMEND oral suspension 25 mg/mL	3 mg/kg orally Maximum dose 125 mg	2 mg/kg orally Maximum dose 80 mg	2 mg/kg orally Maximum dose 80 mg

10. Place the cap on the oral dispenser until it clicks.

11. If the dose is not administered immediately after measuring, store filled oral dispenser(s) in the refrigerator between 2 °C-8 °C for up to 72 hours prior to use. When dispensing dose(s) to the caregiver, instruct them to refrigerate the oral dispenser(s) until they are ready to administer the dose.

12. The oral suspension can be kept at room temperature (not above 30 °C) for up to 3 hours, prior to administration.



Discard any remaining suspension and waste material. Any unused medicinal product or waste material should be disposed of in accordance with local regulations.