SCIENTIFIC DISCUSSION

1. Introduction

Emend is an oral substance P, aka human neurokinin 1 (NK-1)-receptor antagonist. Mammalian tachykinin substance P (SP) that binds to the NK-1 receptor has been associated with numerous inflammatory conditions, mediation of the emetic reflex and modulation of central nervous system disorders. By blocking NK-1 receptors, aprepitant provides a novel mechanism of action for the prevention of induced nausea and vomiting.

On 12 November 2003, the European Commission issued a Marketing Authorisation valid throughout the European Union. The currently approved indication is:

"*Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy. EMEND is given as part of combination therapy".*

The purpose of this variation is to broaden the indication to encompass emetogenic chemotherapies in general. It should be noted that this submission includes one pivotal study conducted in patients treated with moderately emetogenic chemotherapy regimens. No more data has thus been submitted in relation to "highly emetogenic" regimens.

2. Clinical aspects

Rationale for the proposed change

Clinical studies of therapy for Chemotherapy Induced Nausea and Vomiting (CINV) are classified according to either the degree of emetogenicity of the chemotherapy administered or, less frequently, the specific chemotherapy agent or regimen administered. The prototypic highly emetogenic chemotherapy is high-dose cisplatin (>50 mg/m^2), which, in the absence of preventive therapy, causes ≥ 95% of patients to vomit. Agents generally defined as moderately emetogenic chemotherapy include doxorubicin, epirubicin, cyclophosphamide and carboplatin. It should be noted that regimens containing more than one emetogenic agent are more likely to induce symptoms than agents administered alone and that the distinction between highly and moderately emetogenic is not precisely or consistently defined.

A combination of a 5-HT$_3$-receptor antagonist and a corticosteroid administered prior to chemotherapy followed by administration of one or both agents for several days is a recommended regimen for the prevention of CINV after moderate to highly emetogenic chemotherapy regimens. Despite this, the incidence of nausea and vomiting during an initial cycle of chemotherapy is at least 30%. In addition, the efficacy of antiemetic therapy tends to diminish over subsequent cycles of chemotherapy.

In support of the proposed indication, study 071 comparing aprepitant with a standard regimen treatment group was submitted together with a small exploratory study, (044) as discussed in the following sections.

Clinical Pharmacology

Other than biopharmaceutic studies, no new clinical pharmacology data were needed in support of this indication. In order to conduct Protocol 071 in double-blind fashion, the 8-mg tablets of Zofran (ondansetron) included in the comparator regimen were over-encapsulated and placebo ondansetron capsules were made available for the study so, the active ondansetron capsules and the placebo ondansetron capsules were identical in appearance.

An ondansetron bioequivalence study compared the over-encapsulated 8-mg tablet of ondansetron with the unencapsulated 8-mg tablet of ondansetron in order to determine if over-encapsulation altered the biopharmaceutic properties of ondansetron used in Protocol 071.

Results demonstrate that the over-encapsulated tablet and the unencapsulated tablet were bioequivalent with respect to the rate of absorption, but not bioequivalent with respect to the extent of absorption of ondansetron, because the lower limit of the 90% confidence limit (CI) for the geometric mean $AUC_{0-\infty}$ ratio for these 2 formulations (0.796) fell slightly below the lower bound of the bioequivalence limit of 0.80.

Clinical Efficacy

Study 071 is a multi-centre, randomized, double-blind, parallel-group trial to evaluate the efficacy and tolerability of an aprepitant-containing regimen for the prevention of CINV in patients with a diagnosis of breast cancer requiring treatment with non-cisplatin moderately emetogenic chemotherapy regimens that included cyclophosphamide 750 to 1500 mg/m^2, or cyclophosphamide 500 to 1500 mg/m^2 and doxorubicin (≤ 60 mg/m^2) or epirubicin (≤ 100 mg/m^2).

Patient population
Patients with a diagnosis of breast cancer, naive to chemotherapy Hesketh level ≥3, requiring treatment with one of the following moderately emetogenic chemotherapy regimens: I.V. cyclophosphamide (750 to 1500 mg/m^2), I.V. cyclophosphamide (500 to 1500 mg/m^2) and IV doxorubicin (≤60 mg/m^2), I.V. cyclophosphamide (500 to 1500 mg/m^2) and IV epirubicin (≤100 mg/m^2), were included.
The treatment groups were balanced with regard to demographics, type of malignancy, prior and concomitant medications, and chemotherapeutic regimens. Patients were randomized to one of 2 treatment groups as shown in table 1.

Table 1: treatment regimens

Treatment	Day 1	Days 2 to 3
Aprepitant Regimen	Aprepitant 125 mg P.O. once daily Ondansetron 8 mg P.O. twice daily Dexamethasone 12 mg P.O. once daily	Aprepitant 80 mg P.O. daily
Standard Regimen	Ondansetron 8 mg P.O. twice daily Dexamethasone 20 mg P.O. once daily	Ondansetron 8 mg P.O. twice daily

Study endpoints
One *primary efficacy end point* was defined in the protocol to compare the aprepitant regimen and the standard regimen with respect to efficacy in the first cycle of chemotherapy. The primary endpoint was the proportion of patients with complete response, which was defined

as no vomiting and no use of rescue therapy to treat established nausea or vomiting during the 5 days following the initiation of chemotherapy. *Secondary end points* were the effects of aprepitant during the acute and delayed phase of the emetogenic cycle as well as the comparison of the aprepitant regimen and the standard regimen with respect to the Functional Living Index—Emesis (FLIE) questionnaire in the first cycle of chemotherapy.

Clinical response was evaluated with a patient diary that was completed daily for 5 days after the administration of chemotherapy. The diary captured all emetic episodes, all use of rescue therapy, and a daily nausea severity assessment. In an optional multiple-cycle extension, the patient diary was used to capture the daily nausea severity assessment for 5 days after the administration of chemotherapy for each cycle that the patient entered. In addition, on Day 6, the patient recorded whether or not any emetic episodes or nausea occurred since the initiation of chemotherapy as well as any use of rescue therapy (only taken for treatment of established nausea or emesis).

Primary statistical analyses were based on a modified intention-to-treat (mITT) approach. In addition, a supportive per-protocol analysis was done for the primary efficacy parameter. Results are displayed for each endpoint by treatment group and phase (overall, acute, delayed, as well as 0 to 72 hours for nausea endpoints). With 375 evaluable patients per regimen and assuming a true response rate with the standard regimen of 52%, this study would have ~80% power to detect the superiority of the aprepitant regimen, if the true aprepitant regimen effect was 10 percentage points higher than the standard regimen. If the true difference was 12 percentage points, the power would be ~90%.

Results

Baseline patient demographics and characteristics in cycle 1, are presented by each treatment group in table 2a and the overall disposition of patients in table 2b.

Table 2a: Baseline Patient Demographics and Characteristics by Treatment Group—Cycle 1

	Aprepitant Regimen (N=438)		Standard Regimen (N=428)		Total (N=866)	
	N	(%)	N	(%)	n	(%)
Gender						
Male	2	(0.5)	0	(0.0)	2	(0.2)
Female	436	(99.5)	428	(100.0)	864	(99.8)
Age (Years)						
<55	244	(55.7)	260	(60.7)	504	(58.2)
≥55	194	(44.3)	168	(39.3)	362	(41.8)
Mean	53.1		52.1		52.6	
SD	10.7		10.9		10.8	
Median	53.0		52.0		52.0	
Race						
White	349	(79.7)	332	(77.6)	681	(78.6)
Black	34	(7.8)	36	(8.4)	70	(8.1)
Stage of Malignancy						
I	94	(21.5)	95	(22.2)	189	(21.8)
II	252	(57.5)	248	(57.9)	500	(57.7)
IIIa	51	(11.6)	47	(11.0)	98	(11.3)
IIIb	24	(5.5)	20	(4.7)	44	(5.1)
IV	15	(3.4)	14	(3.3)	29	(3.3)
Null	2	(0.5)	4	(0.9)	6	(0.7)

History of Motion Sickness						
Yes	74	(16.9)	90	(21.0)	164	(18.9)
No	363	(82.9)	338	(79.0)	701	(80.9)
Null	1	(0.2)	0	(0.0)	1	(0.1)
History of Vomiting Associated With Pregnancy						
Yes	135	(30.8)	129	(30.1)	264	(30.5)
No	248	(56.6)	250	(58.4)	498	(57.5)
Null	55	(12.6)	49	(11.4)	104	(12.0)

Table 2b: Overall Disposition of Patients—Cycle 1

Time Frame	Aprepitant Regimen N=438	Standard Regimen N=428	Total N=866
Cycle 1	**n=438**	**n=428**	**n=866**
Patient discontinued prior to completion of cycle; reason provided below:	8	7	15
Clinical adverse experience	2	1	3
Lack efficacy	3	2	5
Pt. discont. for other	1	0	1
Pt. withdrew consent	1	4	5
Protocol dev.	1	0	1
Patient discontinued after completion of first cycle; reason provided below:	45	62	107
Clinical adverse experience	5	5	10
Ineligible	3	7	10
Laboratory adverse experience	2	1	3
Lack of efficacy	**17**	**31**	**48**
Noncompliance with treatment	0	1	1
Pt. withdrew consent	16	14	30
Protocol dev.	2	2	4
Refused chemo.	0	1	1
Patient completed and entered next cycle	385	359	744

Efficacy Results

Table 3 presents a summary of the key primary and secondary efficacy results by treatment regimen in **cycle 1**.

Table 3. Number (%) of Patients With Favourable Response in Cycle 1 (mITT)

Efficacy Outcome	Aprepitant Regimen n/m (%)	Standard Regimen n/m (%)	p-Value[†]
Primary endpoint:	220/433 (50.8)	180/424 (42.5)	0.015
No vomiting	327/432 (75.7)	249/424 (58.7)	<0.001

No use of rescue therapy	253/431 (58.7)	237/422 (56.2)	0.480
No nausea (VAS <5 mm)	142/430 (33.0)	140/424 (33.0)	0.903
No significant nausea (VAS <25 mm)	262/430 (60.9)	236/424 (55.7)	0.116

† Aprepitant regimen versus standard regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 years, ≥55 years). Because the endpoints for nausea are exploratory, the p-values shown for these endpoints are for summary purposes only.

No Vomiting = no vomiting or retching or dry heaves.

The complete response rate for the aprepitant regimen group was 50.8%, while a response rate of 42.5% was observed with the standard regimen (p = 0.015).

With respect to complete response in the acute phase (0–24h), there was an almost 7-percentage point difference between the treatment groups (75.7 vs. 69.0%, odds ratio=1.40, p=0.034). During the delayed phase, the advantage for the aprepitant group was smaller and did not reach statistical significance (55.4 vs. 49.1%, odds ratio=1.30, p=0.064).

In the delayed phase (>24 hours to 120 hours post-chemotherapy administration), the complete response rate for the aprepitant regimen was numerically higher than that of the standard regimen, with 55.4% for the aprepitant regimen group and 49.1% for the standard regimen group (p=0.064)

Table 4: No emesis, regardless of use of rescue therapy				**95% CI***
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)

*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.

The aprepitant group had a better outcome with respect to vomiting during both the acute phase (87.5% versus 77.3%; odds ratio=2.07, p<0.001) and delayed phase (80.8% versus 69.1%; odds ratio=1.91, p<0.001) (Table 4).

The estimated time to first emesis in the study is depicted by the Kaplan-Meier plot in Figure 1 and in the figures 2a and 2b the Percentage of Patients with compete Response by day, as well the percentage of patients with no vomiting by day for Cycle 1 is presented.

Figure 1. Kaplan-Meier Curves for Time to First Vomiting Episode From Start of Chemotherapy

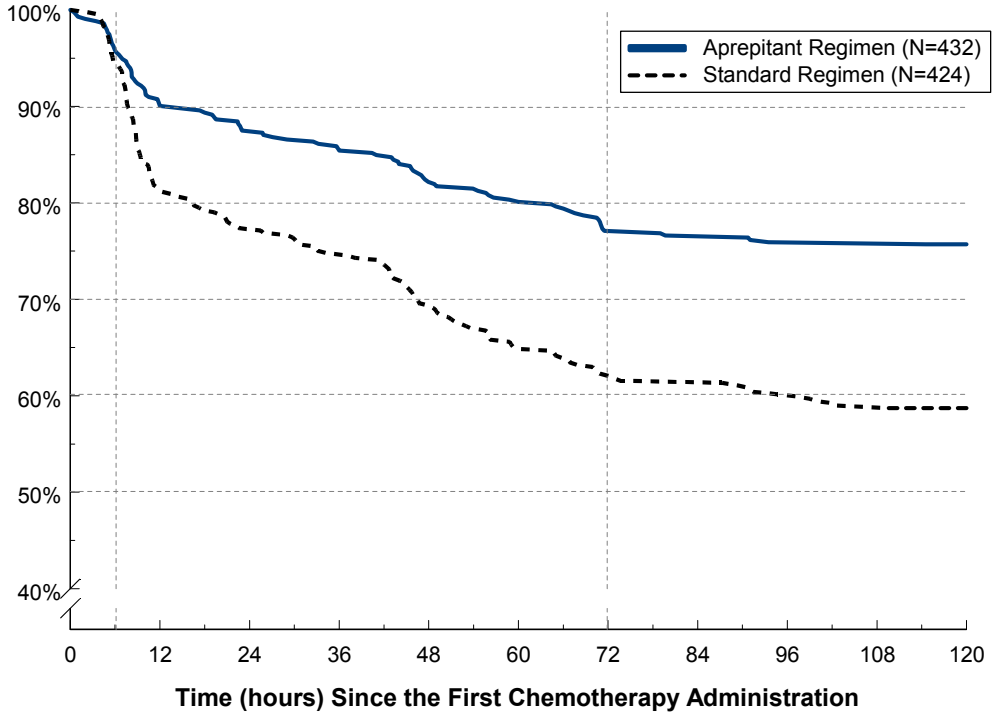

Figure 2a: Percentage of Patients with Complete Response by Day – Cycle 1

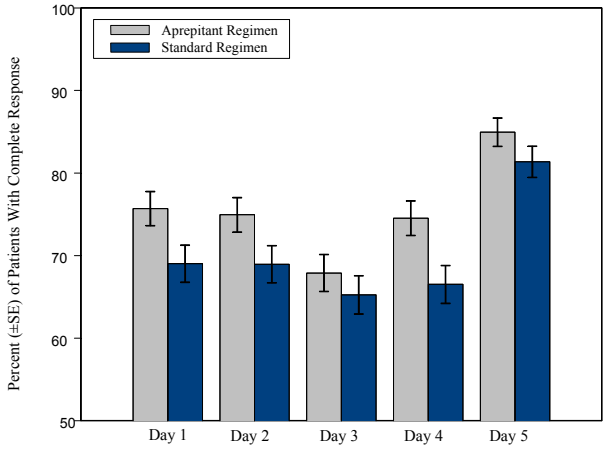

Figure 2b: Percentage of Patients with No Vomiting by Day – Cycle 1

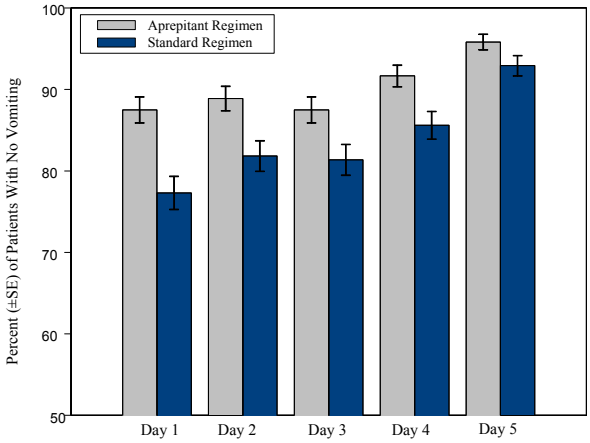

Table 5: Impact on Daily Life (FLIE) (mITT)

	Aprepitant	Standard	p-value
No Impact on Daily Life (FLIE Total)	271/427(63.5)	229/412(55.6)	0.019
Components of Secondary Efficacy Endpoint			
Vomiting Domain	366/427(85.7)	296/412(71.8)	<0.001
"ability to enjoy daily meal"	392/427(91.8)	325/412(78.9)	<0.001
"daily functioning"	394/427(92.3)	329/413(79.7)	<0.001
"hardship on other people"	395/427(92.5)	330/413(79.9)	<0.001
Nausea Domain	229/428(53.5)	210/416(50.5)	0.339

The proportion of patients with no impact of CINV on daily life by treatment group for the Cycle 1 mITT population is shown in table 5. Logistic regression analysis, adjusted for treatment group, investigator group, and age category (<55 year, ≥55 years), was used to determine statistical significance of the treatment difference. As assessed by the FLIE total score, 63.5% of the patients in the aprepitant regimen group reported "no impact on daily life" compared to 55.6% of the patients in the standard regimen group. The treatment difference was significant (p=0.019).

With regard to the percentage of patients with a complete response in cycles 1, 2, 3, and 4 the relevant Kaplan-Meier curves show that the cumulative percentage of patients with a sustained complete response over Cycles 1, 2, 3, and 4 was greater in the aprepitant regimen compared to the standard regimen (p=0.017, Log-rank test). However, as to be expected in the light of the introduced bias the efficacy of both aprepitant and standard treatment increased. Re-randomization prior to, e.g. cycle two would have been appropriate. Although the efficacy (and superiority) seemed to be retained, the data obtained in cycle 2-4 do not allow any conclusions regarding the relative efficacy of the two regimens. Results obtained in the cycles 2-4 are not mentioned in the SPC.

- Supportive study 044.

This is a small (n=55) exploratory study, which was conducted between September 1999 and February 2001. The study was originally planned as a three-armed trial including a dose comparative element (aprepitant 375 vs. 125 mg). The high dose group was closed early after the enrolment of 2 patients and the number of patients to be included was reduced from 900 to about 60. No meaningful information as regards efficacy and safety can be extracted.

Clinical Safety

Protocol 071 randomized 866 patients: 438 patients received the aprepitant regimen and 428 patients received the standard regimen. Of the 438 patients who received the aprepitant regimen, 430 patients completed Cycle 1 and 334 Cycle 4 of chemotherapy. Only safety data from the women included in study 071, were presented.

Adverse events (AE)

As expected in a population receiving chemotherapy, most patients experienced a clinical adverse experience during the study. In Cycle 1 (Table 6), 73.1% of patients receiving the aprepitant regimen and 74.8% of patients in the standard regimen experienced a clinical adverse experience. The treatment groups were similar with respect to the incidence of drug-related adverse experiences (21.5% versus 19.6%), serious adverse experiences (3.4% versus 4.2%), and adverse experiences that led to drug discontinuation (1.6% versus 1.2%) in the aprepitant regimen versus the standard regimen, respectively.

Table 6: Percent of Patients With Clinical Adverse Experiences (Incidence ≥ 3%)—Cycle 1. Event with a difference >1% in Italics

	Aprepitant Regimen (N=438)	Standard Regimen (N=428)
Blood and Lymphatic System Disorders		
Neutropenia	8.9	8.4
Metabolism and Nutrition Disorders		
Anorexia	*4.3*	*5.8*
Psychiatric Disorders		
Insomnia	*4.1*	*5.6*
Nervous System Disorders		
Dizziness	3.4	4.2
Headache	16.4	16.4
Vascular Disorders		
Hot Flush	*3.0*	*1.4*
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal pain	3.0	2.3
Gastrointestinal Disorders		
Constipation	*12.3*	*18.0*
Diarrhoea	5.5	6.3
Dyspepsia	*8.4*	*4.9*
Nausea	7.1	7.5
Stomatitis	5.3	4.4

Skin and Subcutaneous Tissue Disorders		
Alopecia	*24.0*	*22.2*
General Disorders and General Administration Site Conditions		
Asthenia	3.4	3.7
Fatigue	21.9	21.5
All adverse experience terms in Protocol 071 were mapped to MedDRA (Medical Dictionary for Regulatory Activities) version 7.0.		

Among the most commonly reported drug-related events (incidence >2% in one or more treatment groups), only fatigue was reported more frequently in the aprepitant regimen than in the standard regimen (2.5% and 1.6%, respectively). Those events reported more frequently in the standard regimen included constipation (7.7% and 5.7%) and headache (7.2% and 6.4%).
There was no increase in infectious events in the aprepitant arm (9.4% vs. 11.7%). With respect to febrile neutropenia, the incidence was identical cycle 1 (2.1%), but slightly higher cycles 2 to 4 (2.9% vs. 2.2%).
During the multiple cycles of chemotherapy (Cycles 2 to 4), the incidence and pattern of drug-related clinical adverse experiences were essentially similar to those seen in Cycle 1.

Serious adverse events and deaths

No patients in either treatment group died during Cycle 1. One patient receiving the aprepitant regimen died during Cycle 3. This patient died as a result of a serious infection that was not considered by the investigator to be drug related.
In Cycle 1, a slightly higher incidence of serious adverse experiences was reported for the patients receiving the standard regimen (4.2%) compared with patients receiving the aprepitant regimen (3.4%). Two patients in the aprepitant regimen had serious adverse experiences that were considered by the investigator to be drug related (febrile neutropenia and enterocolitis).
Twelve patients discontinued study therapy due to a clinical adverse experience during Cycle 1; 7 patients (1.6%) and 5 patients (1.2%) in the aprepitant regimen and the standard regimen, respectively. Adverse experiences that led to discontinuation of the aprepitant regimen were enterocolitis, nausea, weight decreased, dehydration, headache, migraine, pruritus, rash, and flushing. Adverse experiences that led to discontinuation of the standard regimen were diarrhoea, haematochezia, dehydration, headache, and deep vein thrombosis.

Laboratory findings

During Cycle 1, 12 patients (aprepitant regimen: 4 patients, standard regimen: 8 patients) had a laboratory adverse experience that was deemed by the investigator to be drug related. There were no laboratory adverse experiences that were serious during Cycle 1. No patients were withdrawn from the study (Cycles 1 to 4) due to a laboratory adverse experience.
Laboratory adverse experiences during the multiple cycles were similar to those in Cycle 1 and between treatment groups.

The adverse events profile of the product is heavily influenced by the cytotoxic treatment. The adverse events reported were balanced between treatment arms. No new or unexpected adverse events were reported. The safety profile observed in trial 071 is comparable with those seen in the original application (studies 052 and 054).

Overall Discussion and Benefit – Risk assessment

Although two studies were submitted, only protocol 071 was used in the assessment for this extension of indication. Protocol 071 was a multi-centre, randomized, double-blind, parallel-group trial to evaluate the efficacy and tolerability of an aprepitant-containing regimen for the prevention of CINV in patients with a diagnosis of breast cancer requiring treatment with non-cisplatin moderately emetogenic chemotherapy regimens that included cyclophosphamide 750 to 1500 mg/m^2, or cyclophosphamide 500 to 1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2). Due to methodological difficulties study 044 was not assessable as pivotal nor as supportive study. Also the safety data from this study (044) could not be used in the safety assessment of the product. Therefore only study 071 was adequate for assessment of the benefit/risk of aprepitant in the applied indication.

The possible effect of aprepitant on cyclophosphamide pharmacokinetics was discussed in the original application of Emend. Conclusion at that time was that the data suggest that CYP3A4 does not play a major role in cyclophosphamide metabolism, and that therefore no relevant effect of aprepitant on clinical efficacy of cyclophosphamide containing regimens is to be expected. However, additional data obtained from a recent combination study performed in the Netherlands (de Jong *et al*, 2004[1]) in patients receiving high-dose cyclophosphamide, thiotepa and carboplatin indicated that aprepitant decreased the rate of autoinduction of cyclophosphamide activation to 4-OH cyclophosphamide by approximately 25%. Although the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide AUC only decreased 5% in the presence of aprepitant, the exposure appears to be obtained via lower but sustained plasma concentrations of 4-hydroxycyclophosphamide. It is should be acknowledged that the study group in the de Jong publication is rather small and that the effect of aprepitant on the exposure to 4-HC was mild. However, concerns on the effect of aprepitant on the efficacy of cyclophosphamide treatment of breast cancer remain due to uncertainties with respect to the estimated effect on 4-HC and the impact on curative character of this treatment remain. Comparative efficacy data, of the standard and aprepitant regimen, in terms of CR and PR were not evaluated in study 071 butcomparative safety data, e.g. with respect to grade and duration of neutropenia did not indicate reduced cytotoxicity of cyclophosphamide in the aprepitant group.

Data on *in vitro* inhibition of CYP2B6 in the de Jong publication and in the MAH in house studies differ with IC_{50} 1.3 µg/ml (2.5µm) reported by de Jong and IC_{50} 45 µM reported by the MAH. IC_{50} values are difficult to compare between studies, and Ki values were not reported. With a C_{max} in the range of 3 µM the MAH data suggest a fairly low potential for *in vivo* inhibition of CYP2B6. as the actual *in vitro* studies have not been fully assessed, an effect on CYP2B6 *in vivo* cannot be excluded. In order to facilitate estimation of the possible effect of aprepitant on CYP2B6, follow-up data (notably to determine the Ki value) are needed.

Though the patient population in study 071 was almost exclusively female it has been questioned whether the efficacy of aprepitant in the prevention of emesis can be extrapolated to men across the spectrum of emetogenic chemotherapy regimens. For highly emetogenic courses there is no gender effect. This conclusion was already reached by the CHMP during the assessment of the original application. The problem at hand is the extrapolation of the

[1] de Jonge ME, Huitema ADR, Holtkamp MJ, van Dam SM, Beijnen JH, Rodenhuis S. *Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism*. In: Attemade Jonge ME, ed. Pharmacokinetically guided dosing of (high-dose) chemotherapeutic agents'. Utrecht (The Netherlands): University Utrecht, Faculty of Pharmacy, 2004:191-202 (ISBN 90-9018807-X).

conclusions from these highly emetogenic therapies to moderately emetogenic treatments. Two new elements related to this issue are included in the dossier. First, is shown that the results obtained in women treated with highly emetogenic treatments (Hesketh 5) are not different from those treated with moderately emetogenic therapies. Second, in general literature, a gender difference is not an issue in the discussions about the effects of the various anti-emetic treatment modalities. Although the female gender is accounted as a risk factor for development of vomiting and nausea, the female gender is never related to deviant relative efficacy of any anti-emetogenic treatment modality. Based on this newly submitted information, it seems there is no indication that the product will not have an effect in men.

Study 071 only addresses efficacy and safety of Emend in moderately emetogenic schedules. Due to the small number of patients administered Hesketh level 5 chemotherapy regimens and the absence of glucocorticoid therapy after day 1, no conclusions can be drawn in relation to this subgroup of patients. As no new data concerning highly emetogenic schedules are submitted, the indication should specify that Emend is to be used for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

As regards moderately emetogenic chemotherapies, however, a significant benefit was demonstrated in terms of overall response rate. The results indicate that in study 071 the 'aprepitant regimen' was more effective than the standard regimen with respect to the complete response endpoint, with statistical superiority for the primary end point ($p=0.015$). In the acute phase the results were also statistically superior ($p=0.034$) while in the delayed phase no statistical significance was reached ($p=0.064$). Also considering that the standard therapy (not steroid-containing) was suboptimal to the usual used regimes the data indicate that the efficacy of aprepitant as single agent in the delayed phase is questionable.

Although the effect on nausea appears to be less than that on vomiting (i.e. no superiority could be demonstrated), there are insufficient reasons to distinguish in the indication between the two phenomena. However the data are presented in section 5.1 of the SPC.

Results of the standard therapy were within the expected range as were the results of aprepitant in the overall and acute phase. Results in the delayed phase seemed inferior as (indirectly) compared to the results reported in the high-emetogenic studies (in these studies dexamethasone was added to the regimen during day 2-5), but this may also indicate that platina induced delayed emesis is different from that seen with moderately emetogenic schedules.

No superiority in use of rescue therapy, no nausea or significant nausea could be demonstrated. Impact-on-daily life data indicated a superiority of aprepitant regimen. The nausea data are more or less in line with the results reported in the previous application. The impact-on-daily-life data also show a minor effect on the nausea component. However the overall endpoints (primary and secondary) show statistical significant superiority for aprepitant. These contrasting results are reflected in the SPC in section 5.1.

Efficacy results in multiple cycles must be interpreted with caution due to the fact that patients may have chosen whether or not to continue into the next cycle based on their response in the previous cycle leading to a more favorable response rate in later cycles. Re-randomization prior to, e.g. cycle two would have been appropriate. Although numerical the found efficacy (and superiority) seemed to be retained, the data obtained in cycle 2-4 do not allow any conclusions regarding the relative efficacy of the two regimens. Results obtained in the cycles 2-4 are not mentioned in the SPC.

The adverse events profile is heavily influenced by the cytotoxic treatment. No new or unexpected adverse events were reported. The safety profile observed in trial 071 is comparable with those seen in the original application.

Based on the CHMP review of the above data on safety and efficacy, the CHMP considered that the benefit/risk ratio was favourable and therefore recommended the extension of indication for EMEND:

"Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

EMEND is given as part of combination therapy."