EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2012

EMA/110996/2013
Committee for Medicinal Products for Human Use (CHMP)

Emend

(aprepitant)

Procedure No. EMEA/H/C/000527/A46/0035

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Emend
INN (or common name) of the active substance(s):	aprepitant
MAH:	Merck Sharp & Dohme Limited ("MSD")
Currently approved Indication(s)	EMEND 40 mg: Prevention of postoperative nausea and vomiting (PONV) in adults Emend 80 mg and 125 mg: Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults. Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.
Pharmaco-therapeutic group (ATC Code):	A04AD12
Pharmaceutical form(s) and strength(s):	40 mg capsule, 80 mg capsule, 125 mg capsule, 165 mg capsule
Rapporteur:	Kristina Dunder

I. INTRODUCTION

On June 4, 2012, the MAH submitted a completed paediatric study for Emend, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Emend and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study(ies)

Not specifically stated, but there is nothing indicating that the formulations used differed from the EU licensed hard capsule formulation.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

Study ONO-7436-03: Phase III, multicenter, open-label, uncontrolled study for the prevention of chemotherapy-induced nausea and vomiting

The study was performed to support safety and efficacy of aprepitant in the prevention of chemotherapy-induced nausea and vomiting (CINV) in adolescent Japanese patients aged 12 to 18 years with malignant tumour.

The MAH notes that the study was completed on 3rd March 2011 (LPLV date), but the EMA agreed that the Article 46 procedure should be submitted as soon as the final translation of the clinical study report into English was available.

2. Clinical study

ONO-7436-03 Phase III, multicenter, single arm study for the prevention of chemotherapy-induced nausea and vomiting

- **Description**

This study was conducted by Ono Pharmaceutical Co., a patent licensee of MSD for EMEND (aprepitant), in 8 medical institutions in Japan to evaluate the safety, efficacy and pharmacokinetic for the prevention of CINV in Japanese adolescents.

- **Methods**
  - Study population /Sample size

The study involved 22 Japanese patients aged 12-18 years with malignant tumour who were scheduled to receive chemotherapy including cisplatin, cyclophosphamide, or carboplatin.

- Treatments

The study consisted of a 3-day treatment period and a 12-day follow-up period, and the subjects were observed and examined until Day 15 (the 15th day after the start of study treatment).

Aprepitant was orally administered at 125 mg on Day 1 and 80 mg on Days 2 and 3. On Day 1, aprepitant was administered 1.5 hours prior to the start of the initial highly or moderately emetogenic chemotherapy after breakfast. On Days 2-3, aprepitant was administered after breakfast.

Comment: This is the dose and schedule licensed in adults.

Dexamethasone 4 mg was administered orally days 1, 2 and 3

Granisteron 40 mcg/kg was administered day 1. In addition if highly or moderately emetogenic therapy was administered on further days, granisetron was also administered on chemotherapy days.

- Outcomes/endpoints (selected)

Proportions of patients with Complete Response (no vomiting, no use of rescue therapy) in the overall, acute and delayed phases.

Proportions of patients with Total Control (no vomiting, no use of rescue therapy, and no nausea) in the overall phase.

Proportions of patients (including those who were treated with rescue therapy) with no vomiting in the overall, acute and delayed phases.

- **Results**

- **Pharmacokinetic results**

PK sampling for plasma concentration-time profiles was performed on Day 1, after the 125 mg dose. On Days 2 and 3 only pre-dose (trough) samples were drawn. Pharmacokinetic parameters of aprepitant, such as Cmax, Tmax, AUC, and trough concentration (C24h, C48h, and C72h) were calculated by non-compartmental analysis.

All of 22 adolescent patients (male/female ratio, 13/9; age, 12 to 18 years; body weight, 37.1 to 72.2 kg) were included in the pharmacokinetic analysis population. The pharmacokinetic parameters for Japanese adolescent patients were compared with historical data for adult cancer patients (Study Y06BG013; n=10). Mean AUC and C_{max} were similar in adolescent and adult patients, while the $C_{through}$ values, especially on Days 2 and 3, appeared to be lower in adolescent patients (Table 1). The relationship between PK in adolescents and adults was the same also when the PK parameters were normalised for dose/kg bodyweight (not shown). However, there were large inter-individual differences

in the level of exposure among both adolescent and adult cancer patients, and the range of distribution of PK data for adolescent cancer patients was generally included in that for adult cancer patients.

Table 1. Mean PK parameters for aprepitant in plasma after oral administration of aprepitant 125 mg on Day 1 and 80 mg on Days 2 and 3 to adolescent and adult cancer patients

Patient group	$Cmax_{DAY1}$ (ng/ml)	Tmax (hr)	AUC_{0-24hr} (ng*hr /ml)	C_{24hr}	$C_{48\ hr}$	C_{72hr}
Adolescents (Study ONO-7436-03)	2350 (920)	5,0 (2,0; 2,4)	28100 (10400)	675 (482)	492 (408)	603 (608)
Adults (Study Y-BG013)	2210 (870)	nd	30000 (87000)	1020 (480)	1160 (530)	1340 (680)

Mean (SD) are presented except median (range) for Tmax
n=22, n=10

Assessor's comments:
The approved SmPC for Emend provides the following Day 1 pharmacokinetic parameters for adult subjects (125 mg/80 mg 3-day regimen):
AUC_{0-24hr}: 19600 ± 2500 ng*hr/ml
C_{max}: 1600 ± 360 ng/ml

There is no information in the SmPC on whether race affects aprepitant pharmacokinetics.
No details were provided for Study YBG013 from which the adult data in the comparison were obtained, e.g. whether this study was also performed in Japanese patients. Between-study comparisons of data should be made with some caution.

It is agreed that the new data from study ONO-7436-03 does not warrant any change in the PK section of the EU SmPC.

- **Efficacy results**

Proportion of patients with Complete Response
Overall phase: 10/22
Acute phase: 15/22
Delayed phase: 13/22

Proportion of patients with Total Control
Overall phase: 9/22

Proportion of patients with no vomiting
Overall phase: 14/22
Acute phase: 16/22
Delayed phase: 16/22

Subgroup analyses

Proportion of patients with Complete Response	Male:	5/13
	Female:	5/9
	<15 years	4/8

≥15	6/14
Cisplatin:	2/10
Cyclophosphamide:	6/9
Carboplatin:	2/4

Comment: There are no good reasons to assume that aprepitant would not be efficacious in children 12 – 18 years of age, but the empirical support based on this small single arm study is weak.

- **Safety results**

The incidence rate of adverse events was 100.0% (22/22 subjects), and the incidence rate of adverse drug reactions assumed to be related to aprepitant was 4.5% (1/22). This latter refers to one case of mild abdominal pain.

No clinically significant abnormalities in vital signs, 12-lead ECG, or body weight were observed.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

In the clinical overview supporting this submission, published data are not discussed. Based on a quick search, however, only data of questionable informative value appear available.

In the current SPC it is stated:

"Paediatric population:
The safety and efficacy of EMEND in children and adolescents below 18 years of age has not yet been established. No data are available."
This is strictly speaking no longer true, but the data on pharmacokinetics, efficacy and safety derived from this small, single arm study conducted in Japanese adolescents 12 to 18 years of age are of so limited clinical value that it can be agreed with the MAH that a revision of the SPC is not warranted.

➢ **Recommendation**

x Fulfilled

No further action required

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable