European Medicines Agency
Evaluation of Medicines for Human Use

EMEA/42754/2008

ASSESSMENT REPORT

FOR

IVEMEND

International Non-proprietary Name:
fosaprepitant dimeglumine

Procedure No. (EMEA/H/C/743)

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 3 May 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for IVEMEND, through the centralised procedure falling within the Article 3(2) (a) of Regulation (EC) No 726/2004.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended -complete and independent application.

The application submitted is a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

The applicant applied for the following indication prevention of chemotherapy-induced nausea and vomiting (CINV).

Licensing status
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: Dr Tomas P Salmonson Co-Rapporteur: Dr Barbara van Zwieten-Boot

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 3 May 2006.
- The procedure started on 24 May 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 August 2006 (Annex 4.1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2006 (Annex 4.2). In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 18-21 September 2006, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 September 2006 (Annex 4.3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 8 August 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 September 2007 (Annex 4.4).
- During the CHMP meeting on 15-18 October 2007, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant (Annex 4.5).
- During the meeting on 12-15 November 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to IVEMEND on 15 November 2007. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 06 November 2007 (Annex 4.6.)

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Problem statement
Nausea and vomiting are common adverse effects during or after cancer chemotherapy. Patients consistently report that chemotherapy induced nausea and vomiting (CINV) is an aspect of treatment they find most unpleasant and distressing. This syndrome has a significant impact on patients'

functional status and quality of life and patients may delay scheduled chemotherapy or even on occasion refuse potentially curative therapy because of CINV. The emetic response may be acute (within 24 hours after treatment) or delayed (> 24 hours after treatment). The underlying mechanism(s) of acute and delayed emesis are suggested to be different. Present therapies consist of serotonin 5-HT_3 receptor antagonists such as ondansetron, tropisetron and granisetron and the dopamine receptor antagonist metoclopramide. These compounds have an adequate effect in acute, but not in delayed CINV.

Despite the demonstrated benefits of oral aprepitant, there is still a medical need for treatment options (such as intravenous administration) to prevent CINV in patients who cannot easily tolerate orally administered medication prior to initiating chemotherapy. Parenteral administration is also an important treatment option for oncologists for whom it is frequently more convenient and easier to administer compounds intravenously prior to the administration of chemotherapy (which is also commonly given intravenously).

About the product
The active substance of IVEMEND is fosaprepitant dimeglumine (hereafter referred to as fosaprepitant) is a water-soluble phosphorylated prodrug of aprepitant, which is rapidly converted to aprepitant *in vivo* following intravenous administration. Aprepitant is an antagonist of human substance P neurokinin 1 (NK_1) receptors.

Substance P belongs to the neuropeptide-family, tachykinins and is abundant and widely distributed in the mammalian CNS and other tissues. Its biological action is mediated through G-protein coupled receptors designated NK_1, NK_2, and NK_3. The preferred ligand for the NK_1 receptor is substance P itself. NK_1 receptors are for instance located in brain regions (brain stem nuclei of the dorsal vagal complex) that are critical for the regulation of the vomiting reflex and consequently substance P is able to evoke emesis. The anti-emetic profile of NK_1 antagonists has been demonstrated in several species including ferrets, dogs and pigs. In the most characterised, non-clinical model of emesis, the cisplatin-induced emesis in ferrets, aprepitant showed a good effect on both acute and delayed emesis in contrast to 5-HT_3 antagonists where the effect was seen only in the acute phase. Since fosaprepitant is a prodrug of aprepitant and is rapidly converted in aprepitant, the pharmacological activity of fosaprepitant mirrors those of aprepitant.

The indication applied for IVEMEND by the Applicant is “prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly and moderately emetogenic cancer chemotherapy, including high-dose cisplatin, in combination with other anti-emetic agents”. The proposed regimen of fosaprepitant is 115 mg as a 15-minute infusion administered 30 minutes prior to chemotherapy to substitute 125 mg of oral aprepitant on Day 1.

2.2 Quality aspects

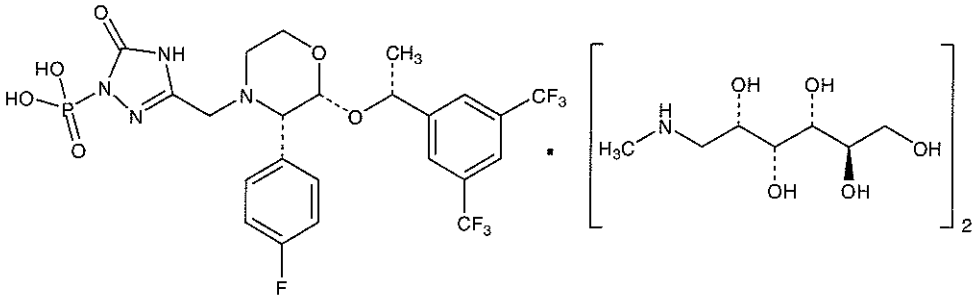
Introduction
Merck Sharp & Dohme Ltd has applied for a marketing authorisation through the centralised procedure for IVEMEND 115 mg powder for solution for infusion.

The active substance fosaprepitant dimeglumine is the water soluble pro-drug of already approved water-insoluble aprepitant (already marketed as a centralised product for the 80, 125 and 40 mg capsules, respectively EMEA/H/C/527 and EMEA/H/C/527/X/015). This new product is intended to be an alternative to the Day 1 oral administration of aprepitant 125 mg. Fosaprepitant converts rapidly to aprepitant *in vivo* following intravenous administration.

The finished product is packaged in a glass vial containing fosaprepitant dimeglumine equivalent to 115 mg fosaprepitant.

The structure of pro-drug fosaprepitant dimeglumine (INN) is detailed below. It is a white to off-white amorphous powder and is very hygroscopic. Properties such as solubility, partition coefficient and

pKa have been described. Fosaprepitant has 3 chiral centres and the counter-ion meglumine 4 chiral centres.



- Manufacture

The synthesis of fosaprepitant can be summarised in 3 main steps starting from aprepitant.

The synthesis has been sufficiently detailed (materials, quantities, temperatures, pressures and typical yields given) including an adequate manufacturing process development.
Satisfactory specifications are provided for all raw materials and starting materials used in the synthesis as well as control of the critical steps and intermediates.

No process validation data has been submitted. However, a formal validation of the manufacturing process, at the proposed manufacturing site will take place prior to release of the product to the market. This was accepted.

Impurities have been extensively discussed, and the level of the impurities (including residual solvents, catalysts and reagents) do not present any toxicological concern.
The structure of fosaprepitant dimeglumine has been elucidated by analytical methods such as UV, IR, NMR (^{1}H and ^{13}C) and MS.

Stereochemistry remains unchanged compared to the starting material aprepitant. The chiral centres of fosaprepitant are controlled in aprepitant as well as the chiral purity of the meglumine counter ion, and no epimerization is expected during the process. Also batch results have been consistent throughout the development and during storage.

- Specification

Adequate specification has been presented for fosaprepitant meglumine and includes parameters such as identification, appearance, assay, related substances, residual solvents, water content, heavy metals, counter ion meglumine.

Analytical methods have been satisfactorily described and validated in accordance with ICH guidelines.

The specification has been justified and in particular the impurity limits. The acceptance criteria for impurities including residual solvents are in line with ICH requirements and batch results and do not raise any safety concern.
Microbiological quality was not included in the specification. It has been appropriately justified taking into account the properties of fosaprepitant, the storage conditions and the manufacturing conditions of the finished product. Optical purity has not been included in the specification since it has been studied and remained stable during storage.

Fosaprepitant dimeglumine is stored in double polyethylene liners in stainless steel containers. Specification for the packaging material polyethylene has been provided and the material complies with EU Directive 2002/72/EC for use with pharmaceuticals.

- Stability

Stability data were provided for pilot (36 months) and commercial (18 months available) batches of fosaprepitant stored in the commercial package at long-term (-20°C) and accelerated (5°C) conditions, in line with ICH conditions.

The following parameters were investigated: appearance, degradation products, assay of fosaprepitant dimeglumine, water content. Analytical methods were described and validated.

Data support a 3 years re-test period when the active substance is kept at -20°C.

Medicinal Product

The product is a sterile lyophilized powder for reconstitution and further dilution prior to intravenous infusion. Each 10-ml vial contains fosaprepitant dimeglumine (equivalent with 115 mg of fosaprepitant free acid) in a lyophilised matrix.

The product is kept in 10 ml Ph. Eur. Type I glass vial with Ph. Eur. rubber stopper and aluminium seal with plastic cap.

- Pharmaceutical development

The finished product is a powder for solution for infusion. The focus of the development has been to provide a parenteral product as an alternative to the oral hard capsule presentation of aprepitant.

Fosaprepitant dimeglumine is a phosphorylated prodrug of aprepitant. Following *i.v.* administration the prodrug rapidly converts to aprepitant. Aprepitant is insoluble in water whereas fosaprepitant dimeglumine is soluble. Fosaprepitant dimeglumine is an amorphous hygroscopic compound that easily degrades to "exclusively" aprepitant unless stored at low temperature. Degradation is enhanced by the presence of water. Therefore conditions of storage at low temperature and reducing the exposure to water have been carefully controlled to avoid conversion to aprepitant before use.

The excipients were selected to provide a physically and chemically stable formulation.

The following compendial excipients (Ph. Eur.) are commonly used for parenteral products and have been used to stabilise the formulation. Edetate disodium prevents precipitation of insoluble salts of fosaprepitant. Polysorbate 80 is added to solubilise the possible degradate and is below a level raising safety concerns. Lactose is added to the formulation to prevent cake collapse. Sodium hydroxide and hydrochloric acid are used for pH adjustment. Water is used as solvent.

Analytical methods are compendial and therefore no validation was needed.

Certificates of analysis in compliance with Ph. Eur. have been presented for each excipient

The manufacturing process development has been extensively discussed. Key steps in the manufacture are compounding, lyophilisation and stopper drying. The process has been optimised to prevent degradation of fosaprepitant during manufacture especially with regard to temperature, pH, and water content.
Since the labile nature of the active substance, terminal sterilisation by moist heat was not feasible. Gamma radiation did also cause degradation of fosaprepitant. Therefore aseptic processing has been the method of choice.

Compatibility between the finished product and the process equipment as well as the packaging materials has been demonstrated. Furthermore, the reconstituted drug product has been tested in medical devices used for reconstitution and administration such as polyolefine syringes, hypodermic needles, *IV* sets, and cannulae.

Compatibility between the finished products and diluents such as 0.9% Sodium chloride injection", "5% Dextrose injection" and "Water for injection" has been confirmed. The product is stated to be incompatible with "Ringer's" and "Lactated Ringer's solutions.

- Adventitious agents

Among the excipients only lactose is from animal origin. A supplier's certificate states that milk is sourced from healthy animals in the same conditions as milk used for human consumption. Therefore it complies with the Note for guidance EMEA/410/01 rev2 and does not present any risk of TSE contamination.

- Manufacture of the product

The manufacturing process has been described in detail (equipment, quantities, temperatures, durations and in-process controls given). The manufacture consists of 11 steps: dissolution of inactive ingredients in water for injections (WFI), cooling, possible pH adjustment, addition of active substance, adjustment of batch weight with WFI, possible pH adjustment, final adjustment of batch weight with WFI, filtration through 0.22 micron filter, filtration into pre-sterilised vials, lyophilisation and capping.

Adequate control of critical steps and intermediates have been applied during the manufacturing process including temperature control, pH check, fill weight check, pre-sterilisation bioburden, filter integrity, control of lyophilisation parameters, and control of the stoppers.

A 5% percent overfill has been included to assure the withdrawal of 115 mg fosaprepitant dimeglumine for reconstitution.

The manufacturing process is not considered as a standard process, given the labile nature of the substance, the water-insoluble nature of the possible degradation product, the lyophilisation step and the aseptic processing. Validation data have been provided for the aseptic part of the process ensuring the sterility of the finished product and validation results submitted for 3 consecutive production batches. Results comply with the release specification and demonstrate the consistency and reproducibility of the manufacture.

The finished product is supplied in type I borosilicate glass vials closed by type I closures (bromo or chlorobutyl rubber stoppers) capped with aluminium seal and a flip-off plastic cap. Glass vials and stoppers have been adequately characterised and comply with Ph. Eur. requirements.

- Product specification

The release and shelf life specification for IVEMEND 115 mg powder for solution for infusion have been provided and include parameters such as: appearance, identification (HPLC, NIR), pH, assay of fosaprepitant (HPLC), related substances (HPLC), uniformity of dosage units (HPLC), water content (NIR, Karl Fischer), particulate matter, sterility, bacterial endotoxins.

Non-compendial analytical procedures have been adequately described and validated.

Analysis of pilot scale batches kept in the commercial packaging have showed that all batches remain within the proposed specification.

- Stability of the product

Eighteen batches of 90 mg/vial, 115 mg/vial, and 150 mg/vial have been kept under long-term conditions (up to 18 months, at 5°C) and accelerated conditions (6 months, at 25°C/60%RH).

The following stability indicating parameters were investigated: assay, degradation product, appearance of solution, particulate matter, pH, reconstitution time, water content.

No significant degradation could be observed under long-term conditions.

Analytical methods were sufficiently detailed and validated.

In general, stability data support the shelf-life and storage conditions as defined in the SPC.

Reconstitution stability data for the drug product support storage for up to 24 hours.

Photostability studies were performed in line with the ICH NfG Q1B showed that the product is not light-sensitive.

The applicant has committed to place the first three production batches under long-term stability until 36 months according to the agreed stability schedule.

Discussion on chemical and pharmaceutical aspects

Generally, satisfactory documentation has been provided. The active substance fosaprepitant (prodrug of aprepitant) is well characterised and the retained specification including the impurities levels have been justified by toxicological studies. Stability data support the proposed re-test period providing that it is kept at -20C.

Regarding the finished product, the manufacturing process is adequately described and controlled. It should ensure a consistent quality for the product. Appropriate specification has been selected for this parenteral product. Stability studies under ICH conditions have demonstrated the good stability of the finished product. Stability data support the proposed shelf life and storage conditions as defined in the SPC as well as stability after reconstitution.

At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide with the necessary information as follow-up measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

2.3 Non-clinical aspects

Introduction

In addition to the pharmacokinetics and *in vivo* metabolism investigations of aprepitant in mice, the pharmacokinetics of fosaprepitant and/or aprepitant were studied in rats and dogs. For the purpose of interspecies comparisons between non-clinical animal models and humans, the plasma protein binding, blood-to-plasma partition ratio and *in vitro* metabolism of [^{14}C]fosaprepitant and/or aprepitant were also investigated. *In vitro* studies were conducted to evaluate the potential of aprepitant to serve as an inhibitor of human cytochrome P450 enzymes and P-glycoprotein-mediated transport and to identify the human liver microsomal P450 enzymes involved in the metabolism of aprepitant.

To support the clinical studies, formulations of fosaprepitant in PS80 (up to 2 mg/ml fosaprepitant and 0.5% PS80) and in saline (up to 50 mg/ml fosaprepitant) were evaluated in non-clinical tolerability and/or toxicity studies. The intravenous fosaprepitant non-clinical studies included *in vitro* and *in vivo* genotoxicity studies, safety pharmacology studies, local tolerance studies, acute and repeated dose (up to 1 month in duration) intravenous toxicity studies in rats, dogs, and monkeys, developmental and reproductive toxicity studies in rats and rabbits, and ocular and dermal irritation studies.

Since fosaprepitant is rapidly dephosphorylated *in vivo* to the active moiety aprepitant following intravenous administration of fosaprepitant, the oral aprepitant studies are included in this Marketing Application including genotoxicity studies, acute and repeated dose (up to 1 year in duration) oral toxicity studies in rats and dogs and developmental and reproductive toxicity studies in rats and rabbits. Based on regulatory guidances (CPMP/ICH/140/95), carcinogenicity studies are not required for indications such as chemotherapy induced nausea and vomiting (CINV) due to the limited, short, and episodic duration of patient treatment. However, carcinogenicity studies in rats and mice as well as the chronic studies in rats and dogs were conducted with aprepitant to support other potential chronic therapeutic indications and are presented for full disclosure.

The pivotal toxicity and safety pharmacology studies (i.e., telemetry in dog and functional observational battery assay in rat) were performed in compliance with Good Laboratory Practices (GLP), as claimed by the Applicant.

Pharmacology

- Primary pharmacodynamics

In vitro receptor affinity

The *in vitro* affinity of fosaprepitant (inhibition of the binding of radioactive natural ligand substance P) is shown in Table 1. The affinity was in all cases lower than for aprepitant.

Table 1. Inhibition of [^{125}I]-Substance P binding to human, dog, ferret, Guinea pig, rat and gerbil NK_1 receptors by aprepitant and fosaprepitant

NK_1 Receptor	Fosaprepitant (IC_{50} nM)	Aprepitant	Ratio (fosaprepitant/aprepitant)
Dog	0.9	0.4-0.5	2
Ferret	1.1	0.5-0.7	2
Human	2.1	0.1	20
Guinea pig	7.5	0.1-0.2	50
Rat	24	3.7-5.5	5
Gerbil	-	0.5	-
Rhesus Monkey	-	0.1	-
Mouse	-	4.7	-
NZW rabbit	-	0.1	-

In addition, the effect of 1% human serum albumin on receptor affinity for the human NK_1 receptor was assayed: the affinity (IC_{50}) decreased 9-fold for fosaprepitant (from 3.3 to 30 nM) and 3-fold for aprepitant (from 0.1 to 0.3 nM). The IC_{50} of aprepitant increased 3-fold with human serum albumin (1%).

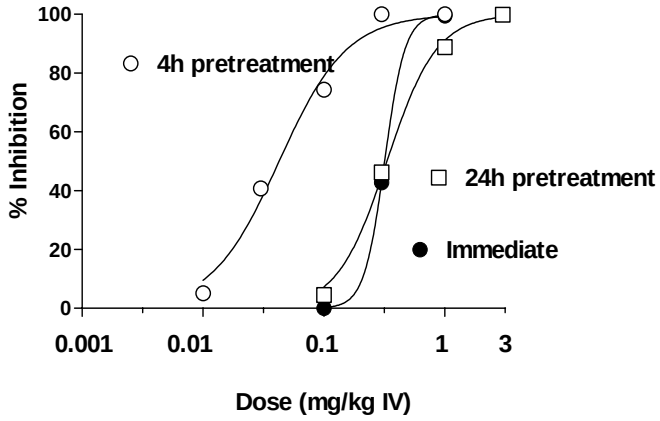
In vitro functional pharmacology

In functional pharmacological assays *in vitro* aprepitant was devoid of agonist activity and had the characteristics of a potent, competitive human NK_1 receptor antagonist. Aprepitant at concentrations up to 10 µM did not stimulate inositol-1-phosphate formation by CHO cells expressing the human NK_1 receptor. Aprepitant consistently attenuated the functional effects of substance P (inositol-1-phosphate formation) at human NK_1 receptors in CHO cells and CHO cells expressing the rat NK_1 receptor (CHO-rNK_1R).

In vivo central NK1 receptor antagonist activity

Central NK_1 receptor antagonist activity *in vivo* was determined by examining the ability of fosaprepitant and aprepitant (intravenously administered) to block repetitive foot-tapping behaviour evoked in gerbils by intracerebral ventricular (ICV) infusion of an NK_1 receptor agonist (GR73632, d-Ala [L-Pro^9, Me-Leu^{10}] substance P) (Figure 1).

Figure 1. Dose related inhibition of NK_1 agonist GR73632 induced foot-tapping in gerbils by aprepitant



Both fosaprepitant and aprepitant had a profile typical of potent brain penetrant NK_1 receptor antagonists with a long central duration of action. When dosed immediately before NK_1 receptor agonist challenge, aprepitant and fosaprepitant produced a dose-dependent and essentially complete inhibition of centrally mediated foot tapping (ID_{50} = 0.32 and 0.95 mg/kg, respectively). Time course studies with aprepitant showed that the central antagonism remained pronounced even when aprepitant was administered 4 or 24 hours before NK_1 agonist challenge (ID_{50} = 0.04 and 0.33 mg/kg, respectively).

In vivo receptor occupancy
Receptor occupancy in brain striatum was studied with PET in anesthetised rhesus monkeys given fosaprepitant intravenous bolus alone (3 or 5 mg/kg, plasma kinetic at 0, 10, 20, 30 and every 30 minutes up to 240 minutes post-dose) or bolus (0.13-2.3 mg/kg) followed by a constant infusion (0.031-0.54 mg/kg/h; plasma kinetic: timepoint 0, 15, 30 and every 30 minutes up to 330 minutes during infusion). The latter protocol gave steady state plasma concentration of aprepitant in the range of 0.035-1.3 µg/ml whereas fosaprepitant concentration was found to be negligible. A 50% receptor occupancy occurred at steady state aprepitant of 0.051 µg/ml and > 80% occupancy at > 0.12 µg/ml. An occupancy of ~90% was measured after bolus dosing of 3 or 5 mg/kg.

In vivo efficacy in emesis model
The anti-emetic activity of the NK_1 receptor antagonist fosaprepitant and aprepitant were examined in a series of studies using two experimental protocols in ferrets. In the first protocol, the ability of fosaprepitant and aprepitant to inhibit the acute emetic effects of cisplatin was assessed over a 4-hour observation period. In the second protocol, the ability of orally dosed aprepitant to inhibit acute and delayed emesis induced by cisplatin in ferrets was determined over a 72-hour observation period following cisplatin administration.

The first studies showed that aprepitant had efficacy against acute cisplatin-induced emesis (ID_{90} for inhibition of retching or vomiting 1 mg/kg IV fosaprepitant and 3 mg/kg P.O. aprepitant) and that anti-emetic effects were enhanced when used in combination with established anti-emetic agents such as dexamethasone or 5-HT_3 receptor antagonists such as ondansetron.

The anti-emetic action of aprepitant was shown to most likely be due to its activity at central sites since it blocked (3 mg/kg P.O.) emesis produced by the centrally acting emetogens morphine and apomorphine, which is refractory to treatment by the 5-HT_3 receptor antagonists.

In a delayed emesis model, no emetic episodes were observed over the entire 72 hours observation period daily after dosing with aprepitant (2 or 4 mg/kg, started 2 hours before cisplatin treatment). At the low dose of 1 mg/kg/day, aprepitant abolished the retching and vomiting response to cisplatin. Inhibition of delayed cisplatin-induced emesis by aprepitant was not a consequence of inhibiting the

acute phase response, as aprepitant was highly effective even when dosing was initiated after the acute emetic response had occurred.

- Secondary pharmacodynamics

The following tests have been carried with fosaprepitant:

In vitro, receptor affinity

Fosaprepitant was tested in a panel of human G-protein coupled receptors (27 different receptors at 1 and 10 μM). Fosaprepitant was > 3000-fold selective for the human NK_1 receptor *versus* the human NK_3 receptor, 818-fold selective *versus* the endothelin A receptor, and > 3000-fold selective *versus* the other receptor tested (including the NK_2 receptor). Fosaprepitant was also shown to be a weak displacer of [3H]-diltiazem at the L-type calcium channel in rabbit skeletal muscle; fosaprepitant IC_{50} = 6 μM, aprepitant IC_{50} = 8 μM.

In vitro, functional pharmacology

Fosaprepitant (1 μM) had no effect on contractile response to a selective NK_2-receptor agonist ($N1e^{10}NKA$) *in vitro* in guinea-pig trachea. Fosaprepitant (1 μM ± vanadate) had no effect on depolarisation of isolated guinea-pig superior cervical ganglia by a selective NK_3-receptor agonist (senktide). Fosaprepitant (1 μM) had no significant effect on calcium entry into depolarised strips of guinea-pig ileum LM/MP. Fosaprepitant (up to 30 μM) were devoid of 5-HT1D-receptor stimulating properties in ring segments of rabbit saphenous vein.

In vivo

Fosaprepitant (5 mg/kg IV) had no effect on changes in CV parameters in anesthetised dog mediated by cholinergic (methacoline, McNeil-343-A, peripheral vagal stimulation), adrenergic (epinephrine, norepinephrine, phenethylsmine), muscarinic (McNeil-343-A), or nicotinic (DMPP) stimuli.

In summary, fosaprepitant showed a high *in vitro* selectivity for the human target receptor *versus* the other tested receptors. Fosaprepitant was tested negative in the functional *in vitro* and *in vivo* tests suggesting no undesirable effects from interference with the non-target receptors investigated.

- Safety pharmacology programme

Fosaprepitant and aprepitant were studied in a range of tests at doses of 1.0 mg/kg intravenously or 5.0 mg/kg orally to assess its potential for effects on cardiovascular/autonomic or respiratory function in anesthetised dogs and renal or gastric acid secretion functional assays in conscious dogs. The cardiovascular effects of fosaprepitant on blood pressure, heart rate, PR-interval, QRS-interval, QT-interval or corrected QT interval (QTcf) were also examined using telemetry in conscious dogs using a Latin square design [each dog received drug vehicle (saline) or fosaprepitant 2, 4 or 6 mg/kg IV with 1-week wash out between each dosing]. Fosaprepitant and aprepitant were also examined in conscious mice at 5.0 mg/kg PO to examine any potential for effects on gastrointestinal motility and at 100 mg/kg PO to evaluate behavioural and other central nervous system effects. In these studies aprepitant did not induce significant effects on cardiovascular, behavioural, central nervous system, respiratory, renal and gastric systems. Importantly, NK_1 antagonism with aprepitant did not induce any relevant effects on gastro-intestinal motility. The minor cardiovascular effects (slight reduction in mean arterial pressure, of heart rate and negligible or no effects on PR, QRS and QTc intervals), that were observed in the safety pharmacology studies were similar to those described with the vehicle. In three repeated dose toxicity studies ECG measurements did not demonstrate any effects on the cardiovascular system in particular on the QT interval at exposures up to 80-fold over clinical exposure.

- Pharmacodynamic drug interactions

The acute anti-emetic effects of aprepitant were studied in combination with ondansetron or dexamethasone and showed that its anti-emetic effect was increased in combination with these anti-emetics.

Cardiovascular effects of diltiazem with fosaprepitant
The potential for cardiovascular changes due to the interaction of fosaprepitant and the L-type calcium channel antagonist diltiazem was investigated in artificially ventilated barbiturate anesthetised dogs. The cardiovascular effects of diltiazem (0.03 to 0.3 mg/kg IV) were similar in saline pre-treated dogs to those pre-treated with 3 mg/kg IV fosaprepitant. At a higher dose of diltiazem (1 mg/kg IV) more sustained cardiovascular effects were seen in fosaprepitant pre-treated animals consistent with 30% higher plasma diltiazem levels. ECG measurements showed changes consistent with AV block following diltiazem 1 mg/kg IV in all dogs regardless of pre-treatment.

Effects of aprepitant on tumour growth and interaction with chemotherapy
Tumour growth was unaffected by aprepitant alone. Moreover, cisplatin-induced inhibition of tumour growth was not attenuated in the presence of active (including aprepitant) or inactive NK_1 antagonists. None of these agents, alone or in combination with cisplatin were overtly toxic. The studies suggest that the use of aprepitant as an anti-emetic will not interfere with the efficacy or enhance the toxicity of cisplatin, nor will it have anti-tumour effects alone.

Pharmacokinetics

The absorption, distribution, metabolism, and excretion (ADME) of fosaprepitant and aprepitant were studied *in vivo* in rat and dog. Metabolism studies were also performed in mouse. Brain penetration studies were performed in rats and ferrets. Toxicokinetic studies were performed as part of the non-clinical toxicity studies in mouse, rat, rabbit, dog and monkey. For interspecies comparisons between non-clinical animal models and humans, protein binding, metabolism, and excretion of fosaprepitant and aprepitant in humans are presented. Most metabolism, excretion, and tissue distribution studies were carried out with [^{14}C]fosaprepitant and [^{3}H]aprepitant or [^{14}C] aprepitant.

- Methods of analysis

Biological samples from studies with radiolabelled compounds were analysed for total radioactivity by liquid scintillation spectrometry. Plasma concentration of fosaprepitant and aprepitant were determined by validated LC-MS/MS methods.

- General

The pharmacokinetic studies following IV administration of fosaprepitant to rats, dogs and humans indicated that the prodrug converted rapidly to the pharmacologically active entity, aprepitant (t_{max}: 0.033 h, plasma concentration undetectable after 15 minutes). Conversion of fosaprepitant into aprepitant in non-clinical species and humans was studied *in vitro* as well as *in vivo*.

In vitro studies indicate that, in addition to the liver, the conversion of fosaprepitant to aprepitant can occur in multiple human tissues.

In vivo, following IV administration in rats and dogs, fosaprepitant maximum aprepitant concentrations were found at 2-5 minutes after administration. In rats, a near proportional increase in the AUC of aprepitant with dose of fosaprepitant was observed after intravenous doses of 1 to 8 mg/kg. The systemic exposure to aprepitant in female rats was 2 to 3-fold greater as compared to male rats. Fosaprepitant was detected only during the first hour post-dose. In dogs elimination started to deviate from linearity at doses above 0.5 mg/kg.

- Distribution

In vitro plasma protein binding
No plasma protein binding studies were performed for fosaprepitant. Binding of [^{3}H]aprepitant to plasma proteins was determined *in vitro* by an ultra-filtration method. [^{3}H]Aprepitant was tightly bound to proteins from rat, dog, and human plasma at concentrations from 0.01 to 10.0 µg/ml. The mean fraction bound was 99.0, 99.3, and 99.7%, respectively. The bound fraction did not vary as a function of aprepitant concentration in any species.

Blood-to-plasma ratio
The blood-to-plasma ratios were determined for aprepitant and were 0.74, 0.55, and 0.62 for rats, dogs, and humans, respectively, following incubations of [^{3}H]aprepitant (0.01 to 10 µg/ml) with fresh, heparinised whole blood from these species. These results indicate that total blood clearance of aprepitant would be somewhat higher than plasma clearance for all three species.

Tissue distribution of fosaprepitant and aprepitant
Following intravenous administration of 2 mg/kg of [^{14}C]fosaprepitant in saline to rats, maximum mean tissue concentrations of radioactivity were observed at 5 minutes through 4 hours post-dose in all studied tissues. The radioactivity concentrations in adrenal gland, liver, kidneys, and thyroid/parathyroid reached a maximum at 5 minutes post-dose. Radioactivity was able to penetrate the blood-brain barrier over time. The testes and brain reached maximum radioactivity concentrations at 4 hours post-dose.

Distribution of [^{14}C]aprepitant after intravenous administration (2 mg/kg) has been studied in rats. Following drug administration, maximum concentrations of radioactivity were observed at 5 minutes through 4 hours post-dose in all tissues, with concentrations steadily declining after reaching C_{max} values. At 5-minute post-dose, concentrations of radioactivity were highest in the adrenal gland, liver, lung, and heart and lowest in testes and brain. By 4-hour post-dose, radioactivity levels in testes and brain reached a maximum when those in heart and liver declined.

After oral aprepitant administration, aprepitant was present as major component in rat and ferret brain, indicating that aprepitant penetrated the blood brain barrier well. In rats a higher portion of radioactivity was due to metabolites than in ferrets. After 48-hour post-dose aprepitant was still present as the major radioactive component in the ferret brain.

Furthermore, one hour after intravenous fosaprepitant administration on gestation Day 20 to pregnant rats and rabbits the foetal plasma concentration was about 10-15% of the maternal plasma concentration. One hour after intravenous fosaprepitant administration in lactating rats, aprepitant concentrations in plasma and milk were similar.

Overall, tissue distribution studies after intravenous administration of radiolabelled fosaprepitant and aprepitant showed that radiolabelled material originating from both compounds distributed rapidly and extensively to tissues, including the brain. Distribution patterns of fosaprepitant and aprepitant were slightly different at the first few time points, but thereafter it was similar. The differences at the first 1–2 time points could be due to the difference in plasma concentration profile in the first minutes after administration (time needed for conversion of fosaprepitant to aprepitant). Aprepitant penetrates the blood brain barrier, crossed the placenta from the maternal compartment and was excreted into the milk of lactating rats.

- Metabolism and excretion

No *in vivo* metabolism data after administration of fosaprepitant to laboratory animals other than those on the conversion to aprepitant were submitted.

After oral administration of aprepitant, metabolism of aprepitant was qualitatively similar in rats, dogs, mice and humans and elimination of aprepitant was mainly by excretion of metabolites. Data on the human metabolite pattern after intravenous administration of fosaprepitant showed no major qualitative differences with the metabolism as found after oral administration of aprepitant to laboratory species.

Aprepitant undergoes N-dealkylation and O-dealkylation resulting in the removal of the triazolone and bis-trifluoromethylphenyl ether sidechains, respectively. Major metabolites present in systemic circulation are mainly nonpolar and polar oxidative products derived from both pathways accompanied by degradation of the morpholine ring. Very polar, low molecular weight acids containing the p-fluorophenyl moiety and glucuronides of oxidative metabolites are major metabolites found in excreta (urine, bile, faeces). Although non-polar metabolites of aprepitant are present in rat brain, intact [^{14}C]aprepitant is the predominant radioactive component in ferret brain 48 hours

following oral dosing. The *in vitro* metabolism of aprepitant is catalysed primarily by CYP3A4, with some involvement of CYP1A2 and CYP2C19.

Excretion of radiolabelled material after administration of radiolabelled fosaprepitant in humans and radiolabelled aprepitant in rat and dog occurred via both the urinary and biliary route. There was no evidence of differences between the species.

- Pharmacokinetic drug interactions

Aprepitant is an inhibitor of CYP3A4 and also an inducer of CYP3A and CYP2C9.

Based on the fact that aprepitant has been demonstrated to be only a weak inhibitor of human P-glycoprotein in *in vitro* systems, the potential for aprepitant to cause adverse drug-drug interactions with chemotherapeutic agents through inhibition of P-glycoprotein mediated transport is anticipated to be low.

Polysorbate 80 was shown to be a weak inhibitor of human MDR1 P-glycoprotein-mediated verapamil and quinidine transport. However, as the IC_{50} values for polysorbate 80 for the inhibition of P-glycoprotein mediated transport are considerably higher than the anticipated peak concentrations after IV dosing of fosaprepitant, it is unlikely that the amounts of polysorbate 80 in the fosaprepitant product will result in significant inhibition of P-glycoprotein *in vivo*.

Toxicology

Toxicity studies provided consist of studies with different formulations of fosaprepitant in PS80 and in saline and studies with oral aprepitant.

- Single dose toxicity

Single dose studies with intravenously administered fosaprepitant showed that the approximate LD_{50} for fosaprepitant injected intravenously as a 1% solution in saline was > 200 mg/kg in rats and > 500 mg/kg in mice. Surviving animals of both species at both dose levels developed local necrotic reactions at the injection site (tail vein). Single oral dose up to 500 mg/kg of fosaprepitant or 2000 mg/kg of aprepitant revealed little to no toxicity.

- Repeat dose toxicity

Intravenous repeated dose toxicity studies with fosaprepitant were carried out in rats (16 days and 5 weeks, dosed up to 10 mg/kg/day), dogs (17 days and 5 weeks, dosed up to 8 mg/kg/day) and monkeys (5 weeks, dosed up to 10 mg/kg/day). In rats, maximum exposure was only a fraction of the proposed clinical dose in humans. In dogs, maximum exposure exceeded the clinical dose in humans with a factor 2-5, in monkeys the maximum exposure was in the range of 1-2 times human exposure.

In the 16-day rat study (formulation: lyophilised fosaprepitant containing EDTA and sodium hydroxide, reconstituted in saline at 25 mg/ml), severe injection site damage was observed at doses of 2.5–7.5 mg/kg/day. At the high dose both sexes showed numerous haematological and serum biochemical changes (decreased erythrocytes, haemoglobin concentration, haematocrit, serum albumin, albumin/globulin ratio, increased reticulocytes, neutrophils, monocytes and platelets). Enlarged lymph nodes at all dose levels in both sexes were considered secondary to treatment-related changes at injection sites.

No drug related effect was found in a 5-week rat study with doses up to 4 mg/kg/day (fosaprepitant dissolved in saline to concentrations up to 0.4 mg/ml).

In another 5-week rat study with doses up to 10 mg/kg/day, with fosaprepitant dissolved at concentrations up to 2 mg/ml in Tween-Sodium Citrate Diluent [= TSCD: containing polysorbate 80 (0.5%), lactose, mannitol, sodium citrate hydrate, citric acid, sodium chloride; ratio of polysorbate 80 to drug: 2.5:1] and diluted further in saline, no injection site damage was found. In this study at 10 mg/kg/day dose slightly increased liver weight and hepatocellular hypertrophy was found, at a

systemic aprepitant exposure of about 0.1-0.3 times the human exposure. This toxicity was similar to that found in oral aprepitant studies.

In the 17-day dog study using lyophilised fosaprepitant (dissolved in saline at 25 mg/ml), injection site damage, body weight loss and decreased food intake was observed at doses of 4 and 6 mg/kg/day. At 2 mg/kg dose, the number of dogs with changes at the injection sites was increased as compared to the vehicle treated control, but the degree of damage was in the range of the normal effect of venipuncture also seen in controls.

In a 5-week dog study testing doses of 0.5, 2, 8 and 21 mg/kg/day of fosaprepitant (dissolved in saline: 0.156, 0.625, 0.5 and 2.0 mg/ml), the two highest dose groups had to be terminated before the end of the study because of local toxicity. At a dose of 2.0 mg/kg no adverse effect was found. The systemic aprepitant exposure at this dose was in the range 0.6–1.1 times the human exposure. An additional 5-week dog study was done with one dose level of 8 mg/kg/day of fosaprepitant (dissolved in saline: 0.625 mg/ml) but this also resulted in local toxicity.

In the monkey study, fosaprepitant dissolved in TSCD did not cause clear adverse effects up to a dose of 10 mg/kg/day. The systemic aprepitant exposure at this dose level was in the range 1.2-2.0 times the human exposure.

In addition, a series of oral repeated dose toxicity studies with aprepitant was submitted. The studies were carried out in rats (16 days and 5, 14 and 27 weeks, dosed up to 2000 mg/kg/day), mice (5 and 14 weeks, dosed up to 2000 mg/kg) and dogs (5, 14 and 39 weeks, dosed up to 1500 mg/kg/day). Maximal exposure multiples achieved were 0.38 and 1.3 in male and female rats respectively, 1.4 and 2.5 in male and female mice, and 40 and 48 in male and female dogs respectively. In monkeys only an intravenous toxicity study was performed with aprepitant (17 days, dosed up to 0.240 mg/kg/day). In rats, there was hypertrophy in the liver and hypertrophy and hyperplasia in the thyroid, presumably caused by microsomal enzyme induction. Serum cholesterol was slightly increased in both sexes and serum triglycerides were slightly decreased in males. Effects on the morphology of erythrocytes were seen at the end of the chronic toxicity study. The salient toxicity findings in the mouse studies were hepatocellular hypertrophy, increase of cholesterol and triglycerides, kidney hydropic tubular degeneration, and decrease of potassium. In dogs, all observed effects occurred at exposures high above human exposure. Effects seen at dosages ≥ 50 mg/kg/day were a decreased food consumption and body weight loss, atrophy in the prostate and signs of degeneration in the testis and increased cholesterol levels. In one study at ≥ 50 mg/kg/day, ovary weight was decreased, without an effect on histopathology. The safety margin for these effects was 8.7 in males and 9.3 in females. Thymus atrophy was found in one study, at dosages ≥ 250 mg/kg/day. No effects were seen in monkeys. However, there was only one intravenous monkey study, in which the maximum dose was very low. Intravenous rat and monkey studies showed no drug related local toxicity, however, only intravenous doses up to 0.240 mg/kg were tested.

- Genotoxicity

Fosaprepitant and aprepitant was found neither genotoxic nor mutagenic based on a series of standard *in vitro* and *in vivo* genetic toxicity assays (gene mutation in bacteria, in mammalian cells, DNA strand breakage, *in vitro* and *in vivo* chromosomal aberrations).

- Carcinogenicity

No studies were conducted with fosaprepitant. Based on regulatory guidances (CPMP/ICH/140/95), carcinogenicity studies are not required for indications such as chemotherapy induced nausea and vomiting (CINV) due to the limited, short, and episodic duration of patient treatment.

- Reproduction toxicity

Effects of intravenous doses of fosaprepitant on male and female fertility, embryofoetal development, and peri- and post-natal development were investigated in rats and effects on embryofoetal development in rabbits at doses up to 4 mg/kg/day of fosaprepitant (except for male fertility in rats: up to 10 mg/kg/day). No adverse effects were found at the tested doses (which were lower than clinical dose).

A similar series of reproduction toxicity studies was done with orally administered aprepitant. No evidence of teratogenicity was seen in rats and rabbits at doses resulting in exposures of 1.1 (rat) and 0.9 (rabbit) times the expected human exposure. In rabbits, post-implantation loss and the number of resorptions per litter were slightly increased at an exposure slightly above the expected human exposure. Signs of maternal toxicity included a small increase in liver weight in rats and increased liver enzymes, decreased triglycerides, decreased food consumption and decreased body weight in rabbits. In rabbits, maternal toxicity was observed at exposures slightly above human exposure (NOEL 5 mg/kg/day). Post-natal mortality of rat pups in a peri- and post-natal development study was slightly increased at an exposure marginally above the expected human exposure. This was predominantly due to mortality on post-natal Days 1-3.

- Toxicokinetic data

Toxicokinetics were assayed in all repeat dose toxicity studies. The exposure levels (mean plasma fosaprepitant and aprepitant) in the highest dosed animals are shown in the Table 2 (the following figures for human exposure were used: fosaprepitant C_{max} = 5.64 µg/ml, AUC = 1.48 µg x hr/ml; aprepitant C_{max} = 2.6 µg/ml, AUC = 30 µg x hr/ml).

Table 2. Summary table of toxicokinetic parameters in different species following intravenous administration of fosaprepitant

Species Study duration Infusion time	**Drug dose (mg/kg/day)**	**Compound**		**Exposure**			**Animal/human exposure ratio**	
				C_{max} (µg/ml)		AUC_{0-24hr} (µgxhr/ml)	**C_{max}**	**AUC**
Rat	5 (7.5)	fosaprepitant	M	0.630	post-injection	0.0312	0.1	0.02
Week 2			F	2’		0.0224	0.1	0.02
Bolus		aprepitant	M	0.487		2.39	0.8	0.08
			F	1.97		5.53	0.6	0.18
				1.54				
Rat	4	fosaprepitant	M	1.069	post-infusion 4’	NC	0.2	-
Week 4			F	1.212		NC	0.2	-
0.25-0.5 min		aprepitant	M	1.069		2.737	0.4	0.1
infusion			F	1.212		5.621	0.5	0.2
Rat	10	fosaprepitant	M	0.0315	post-infusion 4’	NC	0.01	-
Week 4			F	0.0410		NC	0.01	-
0.25-0.5 min		aprepitant	M	2.71		3.85	1.0	0.13
infusion			F	3.36		8.22	1.3	0.27
Dog	6	fosaprepitant	M	16.1	post-injection 2’	0.725	2.9	0.5
Week 2			F	17.7		0.784	3.1	0.5
bolus		aprepitant	M	10.9		98.4	4.2	3.3
			F	12.7		125	4.9	4.2
Dog	2 (32)	fosaprepitant	M	1.01	post-infusion 2’	NC	0.2	-
Week 4			F	2.04		NC	0.4	-
0.5-1 min		aprepitant	M	3.05		31.81	1.2	1.1
infusion			F	2.69		24.78	1.0	0.8
Dog	8	fosaprepitant	M	41.47	during infusion		7.4	-
Week 4				2’		NC	0.2	-
3-5 min			F	1.34	post-infusion 2’		7.6	-
infusion				42.83		NC	0.2	-
		aprepitant	M	1.38			4.4	
				11.52		156.24	5.0	5.2
			F	13.04			5.7	
				14.75		158.08	3.9	5.3
				10.17				
Monkey	10	fosaprepitant	M	16.4	post-infusion 4’	NC	2.9	-
Week 4			F	13.2		NC	2.3	-
1-1.5 min		aprepitant	M	7.80		45.1	3.0	1.5
infusion			F	8.81		60.4	3.4	2.0

NC= not calculated

- Local tolerance

A series of local tolerance studies in rats confirmed the above-mentioned high local toxicity of locally IV infused fosaprepitant, dependent on concentration and composition of the infused solution. None of the tested formulations was the same as the commercial formulation proposed for clinical use.

Significant local reactions were observed from Day 4 at the low dose in rats (2.5 mg/kg/day) and dogs (2 mg/kg/day) receiving fosaprepitant (at 25 mg/ml) as a bolus. The first clinical signs of local reactions were swelling, cutaneous discoloration, induration and desquamation. Various steps were taken in order to investigate the possibility to administer the drug more safely (addition of EDTA or Tween 80 in the infusion solution, using different injection sites, solution dilution, slower infusion rates and/or post-dose catheter flush).

The dogs tolerated a dose of 2 mg/kg when the drug was diluted 40 folds (25→0.625 mg/ml) and given over ~30-60 seconds, but with extensive local reactions occurred after some days at higher dosing. In rat, no local reactions were reported at any dose level tested: up to 4 mg/kg (without Tween 80) diluted 62.5 folds (25→0.4 mg/ml) given over ~15-30 seconds; or up to 10 mg/kg (with Tween 80 0.5%) diluted 12.5 folds (25→2 mg/ml) given over ~15-30 seconds. In monkey, no local reactions were reported up to 10 mg/kg (2 mg/ml given over ~1-1.5 minutes, with Tween 80). Post-dose catheter flush was performed in all studies. Fosaprepitant formulated with Tween 80 was shown to be well tolerated at the infusion site up to 4.3-fold clinical dose, given as a 2-fold concentrated infusion solution and ~10-15 times (monkey) or ~30-60 times (rat) faster than that proposed clinically for IVEMEND.

- Other toxicity studies

No specific non-clinical toxicity studies were conducted to assess antigenicity (no specific reason for such investigation) and immunotoxicity (no evidence in multiple dose studies in rats).

No non-clinical dependence studies were conducted to support a CINV indication because fosaprepitant will be administered as a single dose and will not be used for chronic treatment.

No non-clinical toxicity studies were conducted with metabolites because new metabolites were identified in the non-clinical development (including *in vitro* assays with subcellular fractions from animal liver [HPLC analysis] and pharmacokinetic/toxicokinetic analysis of *in vivo* samples [LC-MS/MS analysis]) and relevant clinical studies.

No special studies on impurities have been performed because each of the specified impurities has been qualified by virtue of having been presented in batches evaluated in the non-clinical toxicity studies and/or by levels allowable under ICH Guidelines for Impurities in New Drug Substances.

A series of non-GLP haemolysis assays was done in rat, dog, monkey and human washed red blood cells and whole blood. Haemolysis in washed red blood cells was found with some of the tested formulations in all tested species, at lower concentrations and more often in rats than in the other species. In whole blood no haemolysis was observed in monkey and human blood, but only concentrations up to 1 mg/ml were tested. With Tween 80, haemolysis occurred at higher concentrations or not at all. This haemolytic effect and the local toxicity of fosaprepitant are assumed to be due to the amphiphilic character of the compound. Polysorbate 80 in the formulation is assumed to protect against this effect.

Ecotoxicity/environmental risk assessment

In the environmental risk evaluation, the PEC value calculated for the EU is below 0.01 µg/l.

Discussion on the non-clinical aspects

In terms of pharmacodynamics, no study was designed to investigate the potential contribution of fosaprepitant to the overall NK_1 receptor inhibitory potency. Since almost a complete in vivo blockade of the target receptor (brain striatum) is expected to have been achieved in the animals studies by

aprepitant/fosaprepitant, a study to investigate the role of fosaprepitant potential contribution is considered not necessary but a mention has been provided in the SPC.

The performed studies on safety pharmacology revealed no concern, the highest IV doses tested were about 2-4 fold of the clinical dose. The systemic exposure to fospaprepitant and aprepitant was however relatively low in the dogs of the telemetry-study (single IV dose up to 6 mg/kg). The potential *in vitro* effect of fosaprepitant or aprepitant on hERG was not studied (in vitro electrophysiology). No such data are requested for the present time being while waiting for the assessment of the requested final report of the clinical QTc study that has recently been undertaken. Only preliminary study data was submitted in the application. A request for additional non-clinical data may later on be triggered according to ICH S7B if the clinical data are considered not sufficient.

The local reactions appeared clinically after some days or at the same day in highly dosed animals (14-fold the clinical dose). Several animals had to be unscheduled sacrificed due to unacceptable injection site reactions. Different ways to overcome the low local tolerability of fosaprepitant were tested: adding compounds to the solution composition and/or change the infusion dosage regimen. Tween 80 was found to improve the local tolerability of fosaprepitant in local tolerance and to reduce the haemolytic property of fosaprepitant *in vitro*. Injection site reactions (induration and pain) were common adverse events in the clinical trials with IVEMEND and the potential risk for significant injection site reactions from accidentally miss-injected drug (e.g. paravenous, intramuscular and subcutaneous) has not been investigated in animals. A non clinical study investigating local tolerance at injection sites is requested as follow-up measure. In meantime, a warning is proposed to be included in the SPC section 4.4 as a precautionary measure. This may be revised dependent on the outcome of the animal study.

For this application, even if the maximum achievable exposure was not fully explored in the low-exposed rats and monkeys, no further toxicity study is required taken into account that substitution with IVEMEND may be considered valuable for some of the patients suffering from severe disease and treated with a highly toxic compound as cisplatin. The limited value of the repeated dose toxicity studies regarding fosaprepitant exposure (AUC), as well as the too high concentration of Tween 80 used in the infusion solution, should be given in the SPC.

No effect on fertility was detected with fosaprepitant. The reproduction toxicity profile of fosaprepitant and aprepitant was evaluated in animals at low exposure, and short duration. No attempts to increase the degree of exposure and the duration of exposure were explored. This circumstance is reflected in the proposed SPC section 4.6. No teratogenicity was evident in the limited studies with fosaprepitant. The approved EMEND should not be used during pregnancy unless clearly necessary, the same recommendation has been proposed for IVEMEND.

2.3 Clinical aspects

Introduction

Twenty six clinical studies were submitted in this application. Table 3 provides synoptic information on those performed with fosaprepitant.

Table 3. List of clinical studies performed with an IV formulation of fosaprepitant

Study number	Study description	Number enrolled	IV Dose Range
	Phase I studies		
P001L1	Multicenter Study: A Double-Blind, Placebo-Controlled, Rising—Single-IV Dose Study to Investigate the Safety, Tolerability, and Preliminary Pharmacokinetics of L-758298 in Healthy Male and Female Volunteers	36	Fosaprepitant mannitol 0.2-100 mg
P005L1	A Double-Blind, Placebo-Controlled, Crossover Study to Investigate the Pharmacodynamics, Safety, Tolerability, and Preliminary Plasma Drug Concentration Profile of L-758298 in Healthy Male Volunteers	16	Fosaprepitant mannitol 0.25-1.43 mg
P009L1	A 2-Part, Double-Blind, Placebo-Controlled, Rising-Single- and Multiple-Dose IV Study to Investigate the Safety, Tolerability, and Pharmacokinetics of L-758298 (Polysorbate 80 Formulation) in Healthy Male and Female Subjects	49	Fosaprepitant PS80 0.25% 25-200 mg
P011	A Double-Blind, Randomized, 3-Period Study to Investigate the Effects of IV L-758298/Oral L-754030 on Diltiazem Pharmacokinetics and Pharmacodynamics in Hypertensive Patients	11	Fosaprepitant mannitol 100 mg
P011L1	A Single Intravenous Rising-Dose Study of the Safety, Tolerability, and Pharmacokinetics of a New Formulation of MK-0517 in Young Healthy Subjects	10	Fosaprepitant non PS80 25-100 mg
P012L1	A Randomized, 5-Part, Intravenous Study of the Safety, Tolerability, Bioequivalence, and Drug Interaction Potential of Final Market Image Formulations of MK-0517 in Young Healthy Subjects	150	Fosaprepitant non PS80/PS80 40-150 mg
P013C1	Absorption, Distribution, Metabolism, and Excretion of C14 MK-0869 Oral and C14 L-758298 I.V. and L-758298 Mass Balance Study	12	Fosaprepitant mannitol ^{14}C-radiolabelled
P016L1	A Double-Blind, Double-Dummy, Randomized, Placebo-Controlled, 3-Period, Single-Dose, Crossover Study to Assess the Effect of MK-0517 on QTc Interval in Healthy Subjects	34	Fosaprepitant PS80 200 mg
P024	Open-Labeled, 5-Period, Crossover Study to Examine the Relationship Between Single Oral Doses of MK–0869 (Colloidal Dispersion) in the Range of 10 to 600 mg and Plasma MK–0869 Concentration, Followed By An Intravenous Arm in Healthy Male and Female Subjects	34	Fosaprepitant mannitol 20 mg
	Phase II CNIV studies		
P004L1	A Double-Blind, Randomized, Active-Agent (Ondansetron)-Controlled, Single IV Dose Study to Investigate the Safety, Tolerability, Plasma Concentrations, and Efficacy of L-758298 in Cisplatin-Induced Emesis	53	Fosaprepitant mannitol 60-100 mg
P007L1	A Double-Blind, Randomized, Active-Agent (Ondansetron Plus Dexamethasone) Controlled Study to Investigate the Safety, Tolerability, and Efficacy of L-758298/L-754030 in Cisplatin-Induced Emesis	177	Fosaprepitant mannitol 100 mg
	Phase II non CNIV studies		
P003L1	A 2-Part, Placebo-Controlled, In-Clinic Study to Explore the Preliminary Safety, Tolerability, and Efficacy of Intravenous L-758298 (An NK1 Receptor Antagonist Prodrug of L-754030) in the Acute Treatment of Migraine	72	Fosaprepitant mannitol 20-60 mg
P006L1	A Double-Blind, Randomized, Placebo-Controlled, 3-Period, Crossover Study to Investigate the Effects of Single Doses of IV L-758298 and Oral Hyoscine on Motion-Induced Nausea in Healthy Male	19	Fosaprepitant mannitol 60 mg
	Phase III PONV safety study		
P015L1	Multicenter Study: A Randomized, Double-Blind, Active Comparator-Controlled, Parallel-Group Study Conducted Under In-House Blinding Conditions, to Examine the Safety and Tolerability of IV MK-0517 for the Prevention of Postoperative Nausea and Vomiting (PONV)	211	Fosaprepitant non PS80 40 mg

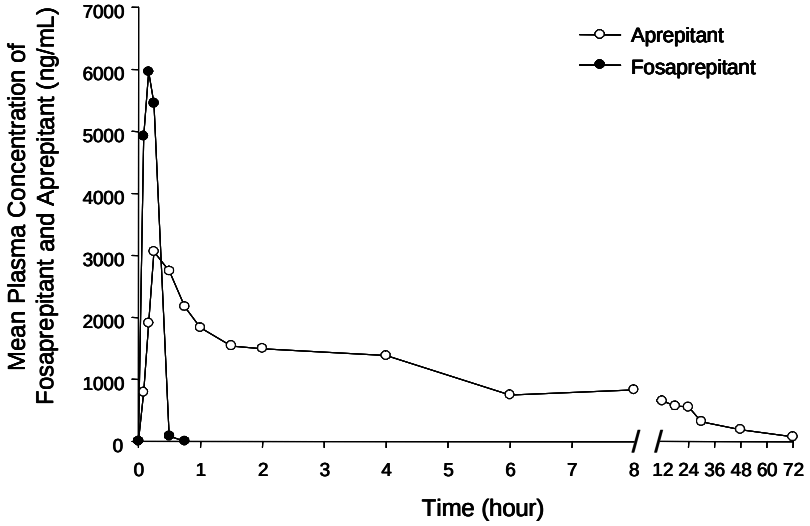
GCP

The clinical overview stated that all studies were conducted following appropriate Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects. A statement on Clinical Requirements has been provided stating that clinical studies conducted outside EU meet the ethical requirements of Directive 2001/20/EC.

Pharmacokinetics

Following administration of a single dose of fosaprepitant 115 mg as a 15-minute infusion to healthy volunteers fosaprepitant is rapidly converted into aprepitant. Fosaprepitant AUC was 1.5 ± 0.3 µg.h/ml and C_{max} (obtained at the end of infusion of fosaprepitant) was 5.6 ± 1.5 µg/ml and aprepitant AUC was 32 ± 14 µg.h/ml and C_{max} (also obtained at the end of infusion of fosaprepitant) was 3.3 ± 1.2 µg/ml. Fosaprepitant levels were below detection limit 30 minutes after the end of infusion (Figure 3).

Figure 3. Study P012L1: Mean plasma concentration of fosaprepitant and aprepitant following a 15-minute infusion of 115-mg fosaprepitant



The mean aprepitant plasma concentration from 4 hours after dosing (including the concentration at 24 hours post-dose) were similar between the 125 mg oral aprepitant dose and the 115 mg intravenous aprepitant dose (Figure 4 on page 27).

- Distribution

Fosaprepitant volume of distribution was estimated to be 5 l. However, the very rapid disappearance of fosaprepitant from plasma possibly reflects the distribution to tissues, where fosaprepitant is hydrolysed to aprepitant. Hence, the estimated volume of distribution is most likely underestimated.

Aprepitant has a high protein binding, i.e., 97-98%. The volume of distribution of aprepitant is ~66 l.

- Elimination

Fosaprepitant clearance and half-life were estimated to 1.3 l/min and 2.3 min, respectively.

Following intravenous administration of 100 mg ^{14}C-labelled fosaprepitant, approximately 57% of the total radioactivity is excreted in the urine and 45% in faeces. No unchanged fosaprepitant or aprepitant is excreted in urine.

Fosaprepitant is eliminated by hydrolysis to aprepitant. Fosaprepitant may be converted to aprepitant efficiently in multiple human tissues. The data provided suggest rapid conversion of fosaprepitant to aprepitant in human liver preparations, but very slow conversion in human blood. Data from S9 preparations from other human tissues suggested similar rate and extent of conversion in liver, kidney and ileum (almost complete conversion within 60 minutes) with slightly slower/lower conversion in lung. The exact identity of the enzyme(s) involved is unknown but is likely related to the phosphoramidase and/or the phosphatase activities observed in a variety of human tissues. Since conversion of the prodrug to aprepitant involves the hydrolysis of the phosphoramide moiety and can occur in the absence of NADPH, conversion of fosaprepitant to aprepitant is not thought to involve the CYP family of enzymes and is unlikely to differ significantly in patient subpopulations.

Aprepitant is eliminated by metabolism (oxidation) to a large number of metabolites. Twelve metabolites of aprepitant have been identified following IV administration of ^{14}C-fosaprepitant. CYP3A4 is the major enzyme involved in the metabolism. Glucoronidation and CYP2C19 may also be involved to some extent. Aprepitant constitutes about 20% of the radioactivity in plasma over 72 hours and is the largest component in plasma during the first 48 hours.

The data do not indicate any other metabolites formed after administration of fosaprepitant than those formed after administration of aprepitant. All of the metabolites have lower or no NK_1 receptor affinity compared with aprepitant and none of the metabolites are likely to contribute significantly to the activity.

- Dose proportionality and time dependencies

Data suggest linear pharmacokinetics of fosaprepitant. Aprepitant pharmacokinetics is non-linear after administration of fosaprepitant with a decreased clearance with increased dose consistent with non-linear PK observed for oral administration of aprepitant.

Time dependency has not been investigated for the final fosaprepitant formulation. No accumulation is to be expected since it is only a single dose treatment and due to the rapid conversion to aprepitant.

- Special populations

Since fosaprepitant is metabolised in various extrahepatic tissues hepatic insufficiency is not expected to alter the conversion of fosaprepitant to aprepitant. Patients with mild hepatic impairment have similar aprepitant pharmacokinetics as healthy volunteers. Conclusions regarding the effect of moderate hepatic impairment on the pharmacokinetics of aprepitant could not be drawn from the data available. Severe hepatic impairment has not been studied.

No new data were provided for this application for fosaprepitant, but based on oral aprepitant data, age, gender, weight, race and renal function have no clinically relevant influence on the pharmacokinetics of aprepitant. Aprepitant is not extracted during haemodialysis. There are no pharmacokinetic data in children.

- Pharmacokinetic interaction studies

Because of the rapid conversion of fosaprepitant to aprepitant, data with regard to interactions for oral aprepitant are also deemed applicable for fosaprepitant. Aprepitant has a complex interaction profile: it is a substrate and inhibitor of CYP3A4 and an inducer of CYP3A4, CYP2C9 and potentially other enzymes.

Two studies were conducted investigating drug-drug interactions with fosaprepitant:

- Fosaprepitant administered as a single, IV dose of 100 mg has no clinically meaningful effect on the pharmacokinetics of midazolam co-administered as a single oral dose of 2-mg (increase in midazolam AUC approximately 1.6-fold). This compares to the 2.3 fold increase in midazolam AUC by 125-mg oral aprepitant.
- In a double-blinded, randomised, placebo-controlled, 3-period fixed sequence study, the interaction between fosaprepitant and diltiazem was investigated in 10 hypertensive patients. Both aprepitant and diltiazem exposures (AUC) after concomitant administration of fosaprepitant with diltiazem were increased by 40-45%. This increase is consistent with moderate inhibition of CYP3A4 both by aprepitant and diltiazem. The effect on diltiazem may be clinically significant.

Specific recommendation for dose reduction of dexamethasone and methylprednisolone is given based on the interaction with oral aprepitant 125 mg. Fosaprepitant has a lower effect on CYP3A4. With the recommended dose reduction of 50% of dexamethasone in combination with fosaprepitant, dexamethasone AUC is expected to be about 20% lower than when dexamethasone is given at its usual dose without fosaprepitant/aprepitant. However, no effect on efficacy is expected due to a flat dose response curve for IV dexamethasone at this dose level.

- Pharmacokinetics using human biomaterials

No clinical pharmacokinetic studies were conducted using human biomaterials.

- Bioequivalence of fosaprepitant and aprepitant

Bioequivalence of fosaprepitant and aprepitant was investigated in the Part V of a multiple-step study (**Study P012L1**) where previous steps led to dose and formulation selection. This Part V was an open-label, randomised, 3-period, crossover study in 75 healthy volunteers using the final market formulation, i.e., containing 0.05% PS80 (administered as a 15-minute constant rate infusion with fosaprepitant at 1 mg/ml). The randomised treatment sequences were:

1) 100-mg intravenous fosaprepitant
2) 115-mg intravenous fosaprepitant
3) 125-mg oral aprepitant

There was a 14-day washout interval between treatment periods. Blood samples (n = 18) were collected for 72 hours following study drug administration for determination of plasma concentrations of aprepitant. Additional blood samples (n = 6) were collected for 45 minutes after administration of fosaprepitant for determination of plasma concentrations of fosaprepitant.

In the primary analysis, aprepitant AUC values following intravenous fosaprepitant doses were adjusted based on the actual dose of fosaprepitant intravenously administered (exact volume of infusate administered multiplied by concentration of infusate). This dose-adjusted analysis was considered the primary analysis in this study to minimise the impact of the dosage administration variability on the assessment of bioequivalence. A supplemental analysis was completed using nominal doses (unadjusted). Secondary pharmacokinetic variables were C_{max}, C_{24h}, t_{max}, and $t_{1/2}$.

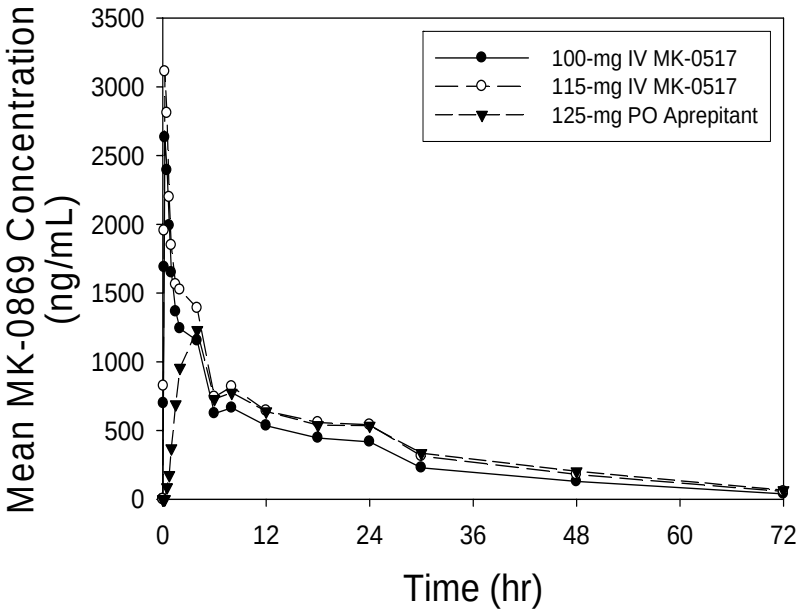
Pharmacokinetic parameters for the 100- and 115-mg dose comparison from this part of the study are displayed in Table 4. Mean aprepitant concentrations are plotted over time in Figure 4.

Table 4. Study P012L1: Pharmacokinetic parameters of aprepitant following administration of 125-mg aprepitant and 100-mg and 115-mg fosaprepitant

	Geometric mean			Geometric Mean Ratio (IV/Oral) (90% CI)		
	125-mg PO aprepitant	**100-mg IV fosaprepitant**	**115-mg IV fosaprepitant**	**100-mg IV fosaprepitant**	**115-mg IV fosaprepitant**	**MSE‡**
$AUC_{0-\infty}$* (ng•h/ml)	26302	22333	29013	0.85 [0.797-0.904] [0.788-0.915]§	1.10 [1.04-1.17] [1.02-1.19]§	0.0479
$AUC_{0-\infty}$† (ng•h/ml)	26318	22889	29611	0.87 [0.82-0.93]	1.13 [1.06-1.20]	0.0471
		Mean ± SD††		**Geometric Mean Ratio (IV/Oral) (95% CI)**		
$AUC_{0-\infty}$† (ng•h/ml)	29215 ± 15731	24961 ± 10477	31724 ± 14287			
C_{max} (ng/ml)	1331 ± 499	2765 ± 1066	3267 ± 1159	2.08 [1.98-2.28]	2.47 [2.25-2.71]	0.0755
C_{24h} (ng/ml)	543 ± 241	424 ± 222	551 ± 267	0.76 [0.69-0.82]	1.02 [0.94-1.11]	0.0600
t_{max} (h)	4.0	0.25	0.25		-	-
$t_{½}$ (h)	14.0	13.0	13.6		-	-

* Results based on nominal dose (unadjusted data for actual IV dose received)
† Results based on dose-adjusted analysis (adjusted data for actual IV dose received)
†† Median for t_{max} and harmonic mean for $t_{1/2}$
‡ Mean square error on natural log-scale
§ 95% CI

Figure 4. Study P012L1: Mean plasma concentration profiles of aprepitant following administration of 125-mg aprepitant, 100- and 115-mg fosaprepitant



The 115-mg rather than the 100-mg dose of fosaprepitant was determined to be more comparable to 125-mg aprepitant based on:

- o C_{24hr} concentration after the 115-mg fosaprepitant dose was more similar to the oral 125-mg aprepitant dose than the 100-mg fosaprepitant dose
- o the dose-adjusted analysis showed that both 100- and 115-mg fosaprepitant were AUC bioequivalent to 125-mg aprepitant but 90% CI of Geometric Mean Ratio (IV/Oral) of unadjusted AUC values of 100-mg fosaprepitant fell out of the bioequivalence bounds of [0.80, 1.25]. Furthermore, the bioequivalence of 115-mg fosaprepitant to 125-mg aprepitant is confirmed in using the 95% CI of Geometric Mean Ratio (IV/Oral) of unadjusted AUC values
- o the safety of the 100- and 115-mg fosaprepitant was comparable. A total of six infusion site reactions were recorded for the 66 subjects who received the 115-mg dose of fosaprepitant *versus* eight infusion site reactions in the 67 subjects who received the 100-mg dose of fosaprepitant.

Plasma concentrations were somewhat higher for 4 hours post-dose for the 115-mg intravenous fosaprepitant dose compared to the 125-mg oral aprepitant dose but similar thereafter.

In conclusion, the data support the 115-mg intravenous fosaprepitant as the strength resulting in the most comparable exposure to aprepitant, as compared to 125-mg oral aprepitant.

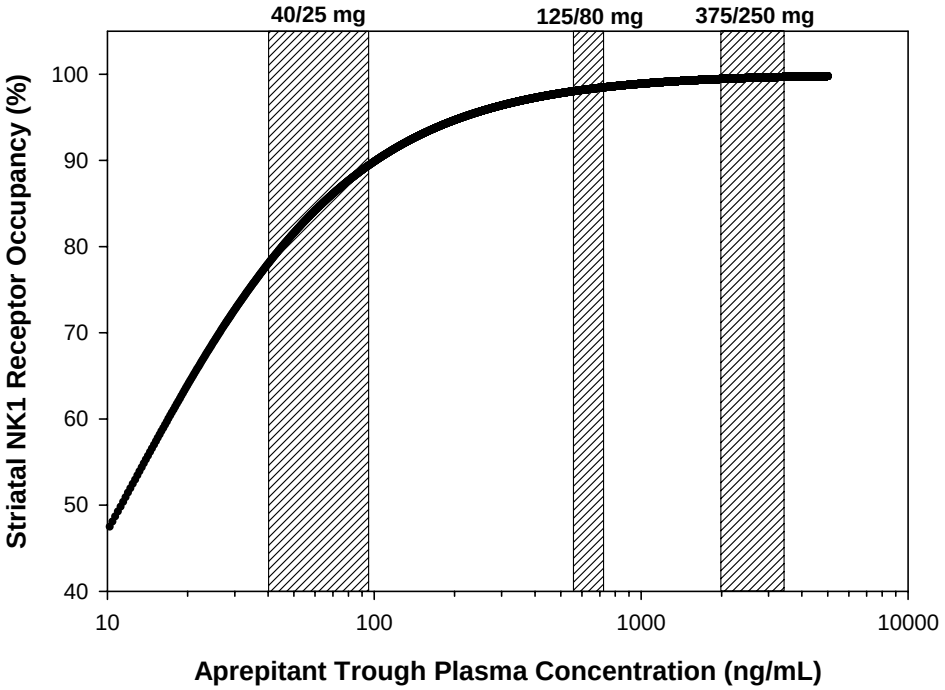
Pharmacodynamics

In non-clinical studies, it has been shown that aprepitant inhibits emesis elicited by centrally acting emetogens. In addition, substance P release in the periphery can elicit an inflammatory response, a response that could be attenuated by an NK_1 receptor-blocking agent. This might be of relevance as mucosal inflammation is assumed to be of importance for delayed emesis. The effect of aprepitant also appears to be more pronounced with respect to vomiting than nausea. Inhibition of NK_1 receptors in vagal motor neurons might therefore also be of relevance as this may prevent fundic relaxation, an early event related to vomiting.

The relationship between plasma concentration and NK_1 receptor occupancy in the CNS has been evaluated in PET studies. Aprepitant plasma concentrations of ~10 ng/ml and ~100 ng/ml produce NK_1 receptor occupancies of ~50% and ~90%, respectively. The aprepitant CINV regimen (125 mg on

Day 1; 80 mg on Days 2 and 3) produces mean trough plasma aprepitant concentrations > 500 ng/ml, which would be expected to result in > 95% brain NK_1 receptor occupancy (Figure 5).

Figure 5. Striatal NK_1 receptor occupancy and ranges of mean trough plasma concentrations of aprepitant



The shaded bars represent the range of the mean trough plasma concentrations of aprepitant achieved on each of Days 1 through 5 with aprepitant 375/250 mg, 125/80 mg, and 40/25 mg regimens in healthy volunteers.

In addition to equivalent in terms of aprepitant AUC, 115-mg fosaprepitant (fosaprepitant PS80 0.05%) produced a C_{24hr} of 504 ng/ml. Based on Figure 3, this trough concentration would result in similar 95% brain NK_1 receptor occupancy. Provided that there is no lag phase, e.g., due to the blood/brain barrier, these data suggest very high receptor occupancy during the entire treatment period.

Clinical efficacy

Since no confirmatory clinical efficacy studies were conducted with fosaprepitant, this section will summarise previously submitted efficacy data obtained with aprepitant for HEC and MEC, highlighting efficacy data using an IV formulation different from that intended to be marketed and similar doses of fosaprepitant and aprepitant at doses higher than the proposed marketed regimen.

- Dose response study(ies)

See section above "Bioequivalence of fosaprepitant and aprepitant"

- Main study(ies)

The clinical programme for aprepitant included two pivotal Phase III studies with similar design. The primary objective was to demonstrate that the add-on of aprepitant to standard therapy (i.e., combination of ondansetron and dexamethasone) is superior to standard therapy alone for prevention of CINV associated with high-dose cisplatin. Both studies were randomised, double-blind, placebo-controlled, parallel-group trials which enrolled a total of 1094 patients receiving chemotherapy that included cisplatin ≥ 70 mg/m^2. The study treatment was aprepitant 125 mg orally on Day 1 plus ondansetron 32 mg intravenously administered on Day 1 plus dexamethasone 12 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4 in the experimental arm and placebo plus ondansetron 32 mg intravenously administered on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4), in the control arm.

Patients were allowed to take rescue therapy for relief of established nausea and/or vomiting. Patients who had taken rescue medication were classified as treatment failures in the primary analysis. Rescue medications were recorded during Cycle 1 only. Assessments of efficacy regarding nausea, emetic episodes and use of rescue medication were recorded by the patient in a diary, from the initiation of cisplatin infusion until the morning of Day 6. Both studies had two components, the initial chemotherapy cycle and an optional multiple-cycle extension, focusing on the initial chemotherapy cycle.

The primary efficacy evaluation was based on evaluation of a composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) over a 120-hour time period following the initiation of cisplatin. Quality of life was measured by patient-reported impact of CINV on daily life using the FLIE (Functional Living Index-Emesis) questionnaire completed on Day 6, *i.e.* 5 days after receiving chemotherapy. In secondary analyses, the overall phase (0-120 hours) was divided into an acute phase (0-24 hours) and a delayed phase (25-120 hours).

The results were evaluated for each individual study and for the two studies combined. A summary of the key study results from the combined analysis is shown in Table 5.

Table 5. Pooled data of studies P052 and P054: Efficacy results, Cycle 1 (mITT)

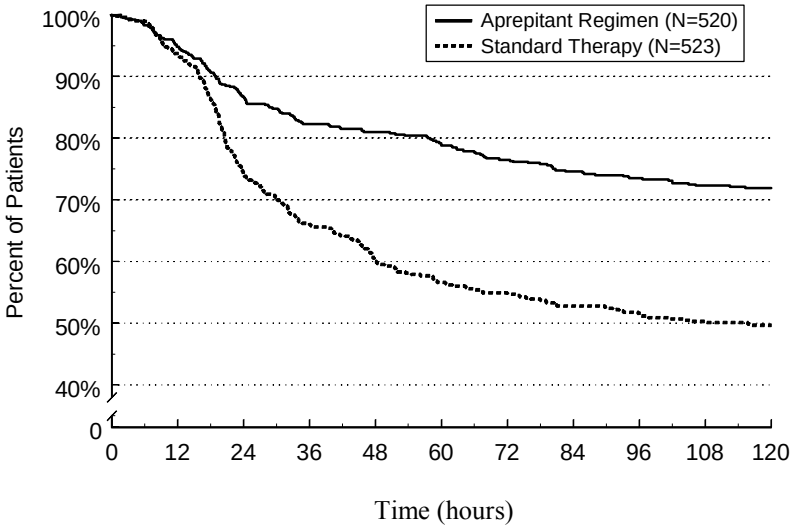
	Aprepitant regimen (n = 521)	**Standard therapy (n = 524)**	**Differences***	
	%	**%**	**%**	**(95 % CI)**
Complete Response (no emesis and no rescue therapy)				
Overall (0-120 hours)	67.7	47.8	19.9	(14.0, 25.8)
0-24 hours	86.0	73.2	12.7	(7.9, 17.6)
25-120 hours	71.5	51.2	20.3	(14.5, 26.1)
INDIVIDUAL 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)
FLIE questionnaire (no or minor impact on daily life)				
Overall (0-120 hours)	74.4	63.9	10.5	(4.8, 16.1)

* 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.

The proportion of patients with an overall complete response (no emesis and no use of rescue medication due to nausea) during the initial chemotherapy cycle (primary endpoint) was statistically significantly higher in the aprepitant group compared to the placebo group in both studies ($p < 0.001$). Statistically significant differences in efficacy were also observed in each individual study.

The estimated time to first emesis in the combined analysis is depicted by the Kaplan-Meier plot in Figure 6.

Figure 6. Pooled data of studies P052 and P054: Kaplan-Meier curve of "who remain emesis free" over time, Cycle 1 (mITT)



In both studies, the Kaplan-Meier curves start to diverge at about 16 hours showing clear effects as add-on to standard therapy as regards delayed emesis.

As regards emesis, the efficacy of aprepitant as add-on to standard therapy has been convincingly demonstrated. In the pooled analysis, a statistically significant effect has also been shown as regards delayed nausea. In the individual studies, the effect on "no significant nausea" defined as < 25 mm on a 100 mm visual analogue scale (VAS), however, was borderline (Table 6).

Table 6. Studies P052 and P054: Efficacy results (nausea), Cycle 1 (mITT)

Endpoint		P052		Difference	P054		Difference
		Aprepitant	Standard	95% CI	Aprepitant	Standard	95% CI
No Nausea	Overall	48%	44%	-5%; +12%	49%	39%	+2%; +18%
	Delayed	51%	48%	-5%; +12%	53%	40%	+4%; +21%
No significant Nausea	Overall	73%	66%	-0%; +15%	71%	64%	-0%; +15%
	Delayed	75%	69%	-0%; +15%	73%	65%	-0%; +15%

In these 2 studies (**Studies P052 and P054)**, 851 patients continued into the multiple-cycle extension for up to 5 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles.

In one randomised, double-blind study (**Study P071**) in a total of 866 patients (864 females, 2 males) receiving chemotherapy that included cyclophosphamide 750-1500 mg/m^2 or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (< 60 mg/m^2) or epirubicin (< 100 mg/m^2), 125 mg aprepitant orally on Day 1 plus ondansetron 32 mg intravenously administered on Day 1 plus dexamethasone 12 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4 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 7.

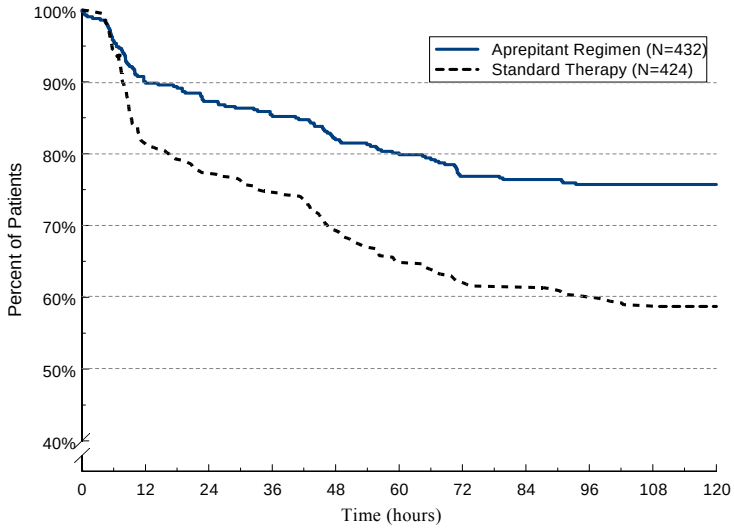
Table 7. Study P071: Efficacy results, Cycle 1 (mITT)

	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)
FLIE questionnaire (no or minor impact on daily life)				
Overall (0-120 hours)	74.4	63.9	10.5	(4.8, 16.1)

* 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 estimated time to first emesis in the study is depicted by the Kaplan-Meier plot in Figure 7.

Figure 7. Study P071: Kaplan-Meier curve of "who remain emesis free" over time, Cycle 1 (mITT)



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

- Analysis performed across trials (pooled analyses and meta-analysis)

See above section "Main studies"

- Clinical studies in special populations

There is no notable difference in efficacy within patient subgroups (age: < 65 *vs.* ≥ 65 and < 75 *vs.* ≥ 75, gender, race: Asian, Black, Hispanic American, Multi-racial, White).

- Supportive study(ies)

Study P004L1 was a clinical Phase IIa study comparing a single 60-or 100-mg dose of fosaprepitant (mannitol containing formulation, not for marketing authorisation) with a single 32-mg dose of ondansetron administered prior to cisplatin 50-100 mg/m^2. In this proof-of-concept study, fosaprepitant was effective in the prevention of both acute and/or delayed CINV (Table 8).

Table 8. Study P004L1: Complete responders during mono-therapy as compared to single dose ondansetron

	Treatment group	
	Fosaprepitant 60 or 100 mg IV n = 30*	**Ondansetron 32 mg IV n = 23**
Overall (Days 1 to 7)	31.0%	21.7%
Acute (Day 1)	36.7%	52.2%
Delayed (Days 2 to 7)	72.4%	30.4%

* Based on an interim assessment of the first 9 patients at the 60-mg dose of fosaprepitant, then this dose was increased to 100 mg

Despite a lower response for acute CINV compared with a 5-HT3 antagonist, a single dose of fosaprepitant given on Day 1 showed efficacy in the delayed phase measured out to Day 7 post-chemotherapy.

Study P007L1 was performed to assess:

- the safety and tolerability of fosaprepitant (mannitol containing, not for marketing authorisation) and aprepitant for the prophylaxis of cisplatin-induced emesis
- the efficacy of fosaprepitant plus dexamethasone in the acute phase (first 24 hours) of cisplatin-induced emesis
- whether a single dose of fosaprepitant plus dexamethasone followed by 4 days of aprepitant or placebo will prevent delayed emesis (Days 2 to 5 post-cisplatin infusion) and
- whether a single dose of fosaprepitant plus dexamethasone followed by 4 days of aprepitant or placebo will reduce nausea following cisplatin (Days 1 to 5 post-cisplatin infusion).

This randomised, double-blind, active-controlled (ondansetron plus dexamethasone) study in 177 cisplatin-naïve patients with various cancer type evaluated the prevention of both acute (0 to 24 hours) and delayed (Days 2 to 5) emesis after cisplatin IV (≥ 70 mg/m^2).

All patients received dexamethasone 20 mg intravenously before cisplatin. In addition, patients were randomised to 1 of 3 groups to receive:

Group A	n = 62	fosaprepitant 100 mg intravenously prior to cisplatin and aprepitant 300 mg once daily on Days 2 to 5
Group B	n = 57	fosaprepitant 100 mg intravenously prior to cisplatin and placebo once daily on Days 2 to 5
Group C	n = 58	ondansetron 32 mg intravenously prior to cisplatin and placebo once daily on Days 2 to 5

Rescue therapy was permitted on an as-needed basis at any time for all patients but was not to be given prophylactically. Randomisation was stratified both for gender and for moderate to highly emetogenic chemotherapy given in addition to cisplatin.

Episodes of vomiting or retching (date, time and number of episodes) were recorded by the patients on diary cards. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches; distinct episodes were separated by at least 1 minute. Emetic episodes were recorded daily in a patient diary. The primary efficacy parameter was the proportion of patients with no emesis (i.e., no emetic episodes) in the acute phase (0 to 24 hours post-initiation of cisplatin infusion). Emetic episodes in the delayed phase (24 to 120 hours post-initiation of cisplatin infusion) and the use of rescue medication in both periods were also evaluated. In addition, the proportion of

patients (complete responders) with no emesis and no rescue therapy during the acute and delayed phases was a post-hoc exploratory efficacy parameter.

Patient self assessment of nausea was assessed every 24 hours in the patient diary using a 100-mm horizontal VAS. Global satisfaction with the anti-emetic treatment was assessed by the patient the morning of Day 2 and the morning of Day 6 post-cisplatin using a 100-mm VAS.

During the acute phase, the treatment providing the best control of emesis was the standard therapy (ondansetron plus dexamethasone - Group C). Table 9 provides the results of the primary analysis.

Table 9. Study P007L1: Effect on emesis in the acute phase

	Treatment group			
	A	B	A + B	C
Response criteria category	**n = 60**	**n = 57**	**n = 117**	**n = 58**
No emesis	50.0%	45.6%	47.9%*	84.5%
1 to 2 emetic episodes	23.3%	26.3%	24.8%	10.3%
3 or more emetic episodes	26.7%	28.1%	27.4%	5.2%

* Significantly different from group C

The difference between the combined group (Groups A and B) and Group C was -36.6%, with a 90% CI about this difference of -49.6 to -24.2%. Furthermore, an additional exploratory analysis showed that the proportion of patients without emesis and no use of rescue therapy in Group C (82.8%) was higher than either Group A (45.0%), Group B (35.1%), or the combined group (Groups A and B) (40.2%; $p < 0.001$ for Group C *vs.* the combined groups).

During the delayed phase, the best control of emesis was achieved in those patients who received an NK1-receptor antagonist, administered either at Days 1-5 or only at Day 1 (Table 10).

Table 10. Study P007L1: Effect on emesis in the delayed phase

	Treatment group		
	A	B	C
Response criteria category	**n = 60**	**n = 57**	**n = 58**
No emesis	66.1%*	60.7%*	41.4%
1 to 2 emetic episodes	18.6%	17.9%	17.2%
3 or more emetic episodes	15.3%	21.4%	41.4%

* p-value < 0.001

The between-treatment difference was (24.7%) with 95% CI of 5.9 to 43.6% for Groups A and C and 19.3% with 95% CI of 0.4 to 38.8% for Groups B and C. An exploratory analysis showed a similar advantage in the proportion of patients without emesis and no use of rescue therapy in the delayed phase (59.3, 44.6, and 37.9% in Groups A, B, and C, respectively; Groups A *versus* C were significantly different, $p < 0.05$).

- Discussion on clinical efficacy

The pharmacokinetics of fosaprepitant has been adequately evaluated. Upon I.V. infusion over 15 minutes, fosaprepitant is rapidly converted in aprepitant. Bioequivalence with respect to aprepitant AUC between 115-mg fosaprepitant and 125-mg aprepitant has been demonstrated.

No formal pharmacodynamic studies on fosaprepitant were submitted however the pharmacodynamic properties of the active metabolite aprepitant were appropriately evaluated. The aprepitant studies showed that there is a relation between plasma concentration of aprepitant and the NK1-receptor occupancies in the brain and a beneficial treatment effect on delayed emesis.

No confirmatory study was conducted with fosaprepitant and is considered adequate in view of the pharmacokinetic and pharmacodynamic data for fosaprepitant and aprepitant.

Clinical safety

Clinical safety profile of fosaprepitant is supported by data collected during clinical studies performed with fosaprepitant and with high dose of oral aprepitant since fosaprepitant is rapidly converted in aprepitant and produces plasma concentration similar to high dose of oral aprepitant.

Safety of fosaprepitant

- Patient exposure

All together 696 individuals have been exposed to fosaprepitant IV of whom 123 received the market formulation and 76 individuals to a dose of 115 mg or higher.

The exposure to fosaprepitant by formulation is outlined in Table 11 and while Table 12 provides exposure by dose.

Table 11. Subject and patient exposure to fosaprepitant by formulation

	Fosaprepitant mannitol†	Fosaprepitant PS80 0.25%‡	Fosaprepitant nonPS80§	Fosaprepitant PS80 0.05%‖	All Formulations
Phase I	98	35	58	123	314
Phase II CINV	149				149
Phase II Non-CINV	66				66
Phase III Non-CINV			167		167
Total Exposure:	313	35	225	123	696

Table 12. Subject and patient exposure to fosaprepitant by dose

	Number of subjects/patients exposed							
	Any dose	< 90 mg	90 mg	100 mg	115 mg	120 mg	150 mg	200 mg
Market formulation	123	0	34	89	66	0	10	0
All formulations	696	383	34	306	66	6	39	17

Subjects/patients are counted once for each dose received
All subjects/patients counted in the “Market formulation” row are also counted in “All formulations" row

- Adverse events

This section will focus on tolerability data of the market formulation in the population in which it was tested (healthy subjects) and tolerability data in the patient population (CINV) where it is intended for use (using a previous formulation). It must be emphasised that the exposure to fosaprepitant itself is brief (undetectable by 30 minutes), although fosaprepitant plasma levels average 5800 ng/ml at the end of a 15-minute infusion with a 115-mg dose of the market formulation.

Intravenous fosaprepitant including local tolerability

Fosaprepitant has been generally well tolerated with a low incidence of adverse events, including adverse events that occur at the infusion site. The incidence of adverse events among healthy subjects receiving the market formulation of fosaprepitant is in Table 13; of note, subjects who received aprepitant 125 mg did not receive an intravenous placebo administration.

Table 13. Study 012L1: Number (%) of subjects with at least one adverse event exposed to market formulation of fosaprepitant

	Fosaprepitant < 115 mg (N = 115)		Fosaprepitant 115 mg (N = 66)		Fosaprepitant 150 mg (N = 12)		Aprepitant 125 mg (N = 133)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse events	17	(14.8)	7	(10.6)	3	(25.0)	6	(4.5)
Gastrointestinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(8.3)**	**1**	**(0.8)**
Nausea	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
General disorders and administration site conditions	**8**	**(7.0)**	**5**	**(7.6)**	**1**	**(8.3)**	**0**	**(0.0)**
Infusion site erythema	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion site induration	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Infusion site pain	7	(6.1)	5	(7.6)	0	(0.0)	0	(0.0)
Tenderness	1	(0.9)	0	(0.0)	1	(8.3)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(8.3)**	**0**	**(0.0)**
Contusion	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(8.3)**	**0**	**(0.0)**
Intraocular pressure test	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)
Nervous system disorders	**9**	**(7.8)**	**2**	**(3.0)**	**2**	**(16.7)**	**6**	**(4.5)**
Dizziness	3	(2.6)	0	(0.0)	0	(0.0)	1	(0.8)
Headache	6	(5.2)	2	(3.0)	2	(16.7)	5	(3.8)
Reproductive system and breast disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(8.3)**	**0**	**(0.0)**
Dysmenorrhoea	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Rash	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)

The possibility of reactions at the site of infusion of the market formulation was carefully assessed because previous fosaprepitant formulations have been associated with local reactions, which were dose, infusion rate, and formulation dependent. Although the market formulation contains the solubilising agent PS80 which has been associated with hypersensitivity reactions. The concentration of PS80 in the market formulation is significantly lower (0.05%) than in an earlier fosaprepitant formulation (0.25%) and also lower than in other marketed products such as the taxane chemotherapy agents. The lower PS80 concentration in the fosaprepitant formulation for market should have a low likelihood of hypersensitivity reactions. In an earlier study, using the fosaprepitant PS80 0.25% formulation, 1 of 35 subjects had a hypersensitivity reaction. Of note, no hypersensitivity reactions were noted in 123 subjects who were administered the market formulation of fosaprepitant. The likelihood of hypersensitivity reactions is further diminished by the co-administration with dexamethasone as part of the CINV regimen.

Safety experience in CINV patients (intravenous fosaprepitant mannitol)

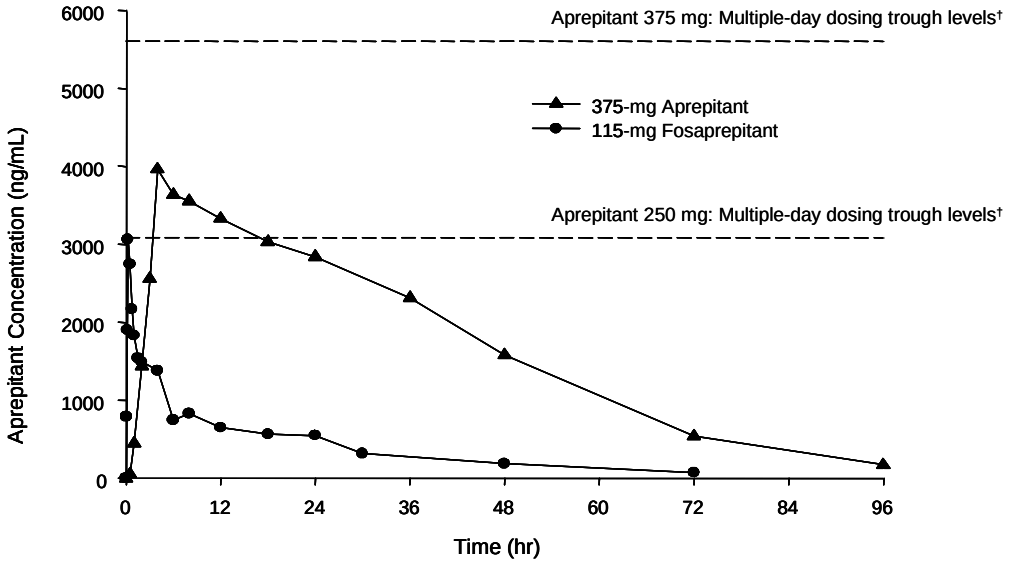
In two clinical CINV studies, a total of 140 patients received fosaprepitant mannitol 100 mg; an additional 9 patients received 60 mg (administered 1 hour prior to initiation of cisplatin-based). In these studies, fosaprepitant was generally well tolerated compared with ondansetron with or without the use of other anti-emetic agents. Additionally, infusion site intolerability was reported infrequently.

Safety of high dose oral aprepitant

Aprepitant plasma exposure at or in excess of that provided by the market formulation of fosaprepitant has occurred in patients in the Phase III depression programme (i.e. the programme evaluating aprepitant as an anti-depressant), patients at risk for CINV in the Phase II programme and healthy young subjects in a multiple-dose pharmacokinetic study As illustrated in Figure 8, a single oral dose of the aprepitant 375-mg capsule provides a plasma level at C_{max} greater than the aprepitant C_{max} which occurs with single IV dose fosaprepitant. Figure 6 also shows how the aprepitant trough plasma

levels associated with repeat dosing of oral aprepitant 375 mg and 250 mg exceed the level associated with a single IV dose of fosaprepitant.

Figure 8. Mean plasma aprepitant levels following 15-minutes IV infusion of 115-mg fosaprepitant in regard to oral aprepitant doses



† Trough concentrations for daily, oral doses administered in the Depression program (Week 3)

Oral aprepitant 250 or 375 mg was administered daily for 8 weeks to 180 patients in a placebo-controlled depression study (**Study 039**). Both aprepitant doses provide a greater plasma exposure than the peak plasma aprepitant exposure resulting from a single IV dose fosaprepitant. Both aprepitant doses were well tolerated relative to the control; in this depression study, there were no serious adverse events associated with aprepitant. There was no pattern among the types of clinical adverse event that caused discontinuation in patients receiving either dose of aprepitant in this prolonged exposure to high doses. A higher percentage of patients receiving aprepitant 250 mg (16.5%), aprepitant 375 mg (13.5%) and paroxetine (15.1%) discontinued treatment due to an adverse event compared with placebo (1.1%). Table 14 displays adverse events with an incidence ≥ 5%.

Table 14. Study 039: Summary of adverse events (incidence ≥ 5%) following repeated 250- or 375-mg aprepitant oral administration

	Aprepitant 250 mg (N=91)		Aprepitant 375 mg (N=89)		Paroxetine 20 mg (N=86)		Placebo (N=92)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	67	(73.6)	66	(74.2)	73	(84.9)	62	(67.4)
Body as a whole/Site unspecified	**34**	**(37.4)**	**36**	**(40.4)**	**32**	**(37.2)**	**26**	**(28.3)**
Abdominal pain	2	(2.2)	6	(6.7)	4	(4.7)	3	(3.3)
Asthenia/fatigue	5	(5.5)	8	(9.0)	8	(9.3)	3	(3.3)
Dizziness	13	(14.3)	7	(7.9)	5	(5.8)	2	(2.2)
Influenza-like disease	4	(4.4)	5	(5.6)	6	(7.0)	3	(3.3)
Upper respiratory infection	13	(14.3)	13	(14.6)	8	(9.3)	13	(14.1)
Digestive system	**25**	**(27.5)**	**31**	**(34.8)**	**42**	**(48.8)**	**30**	**(32.6)**
Diarrhoea	8	(8.8)	6	(6.7)	12	(14.0)	8	(8.7)
Dry mouth	9	(9.9)	9	(10.1)	12	(14.0)	6	(6.5)
Nausea	9	(9.9)	11	(12.4)	22	(25.6)	6	(6.5)
Vomiting	0	(0.0)	1	(1.1)	4	(4.7)	4	(4.3)
Eyes, ears, nose, and throat	**11**	**(12.1)**	**12**	**(13.5)**	**9**	**(10.5)**	**8**	**(8.7)**
Pharyngitis	4	(4.4)	5	(5.6)	0	(0.0)	1	(1.1)
Musculoskeletal system	**9**	**(9.9)**	**11**	**(12.4)**	**11**	**(12.8)**	**6**	**(6.5)**
Back pain	1	(1.1)	5	(5.6)	6	(7.0)	1	(1.1)
Nervous system	**27**	**(29.7)**	**32**	**(36.0)**	**34**	**(39.5)**	**27**	**(29.3)**
Headache	12	(13.2)	18	(20.2)	14	(16.3)	13	(14.1)
Insomnia	4	(4.4)	2	(2.2)	14	(16.3)	7	(7.6)
Somnolence	13	(14.3)	13	(14.6)	9	(10.5)	7	(7.6)
Psychiatric disorder	**9**	**(9.9)**	**5**	**(5.6)**	**15**	**(17.4)**	**9**	**(9.8)**
Anxiety	0	(0.0)	3	(3.4)	1	(1.2)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	4	(4.7)	0	(0.0)
Skin and skin appendages	**8**	**(8.8)**	**7**	**(7.9)**	**2**	**(2.3)**	**7**	**(7.6)**
Rash	1	(1.1)	6	(6.7)	0	(0.0)	1	(1.1)
Urogenital system	**9**	**(9.9)**	**11**	**(12.4)**	**26**	**(30.2)**	**8**	**(8.7)**
Ejaculation function disorder	1	(2.1)	1	(2.5)	3	(8.6)	0	(0.0)
Erectile dysfunction	0	(0.0)	0	(0.0)	2	(5.7)	0	(0.0)
Libido decreased	2	(2.2)	3	(3.4)	7	(8.1)	1	(1.1)
Menstrual disorder	2	(4.7)	1	(2.0)	1	(2.0)	0	(0.0)
Orgasmic dysfunction	1	(1.1)	3	(3.4)	8	(9.3)	1	(1.1)
Sexual dysfunction	0	(0.0)	1	(1.1)	4	(4.7)	0	(0.0)

A Phase II CINV study (**Study 040/042**), provides important comparative safety data. In this study, the aprepitant 375-mg dose (375/250 mg) was well tolerated and was similar to aprepitant 125-mg dose (125/80 mg) regimen (Table 15).

Table 15. Study 040/042: Summary of adverse events (incidence ≥ 5%) following various oral aprepitant regimens

	Aprepitant regimen plus Standard Therapy						Standard Therapy	
	375 mg (N=34)		125 mg (N=214)		40 mg (N=120)		(N=212)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	29	(85.3)	162	(75.7)	85	(70.8)	152	(71.7)
Body as a whole/Site unspecified	**17**	**(50.0)**	**93**	**(43.5)**	**45**	**(37.5)**	**80**	**(37.7)**
Abdominal pain	0	(0.0)	14	(6.5)	4	(3.3)	7	(3.3)
Asthenia/fatigue	7	(20.6)	43	(20.1)	15	(12.5)	35	(16.5)
Chest pain	2	(5.9)	9	(4.2)	6	(5.0)	11	(5.2)
Dehydration	3	(8.8)	20	(9.3)	8	(6.7)	13	(6.1)
Dizziness	3	(8.8)	14	(6.5)	8	(6.7)	13	(6.1)
Mucous membrane disorder	2	(5.9)	10	(4.7)	6	(5.0)	7	(3.3)
Digestive system	**19**	**(55.9)**	**104**	**(48.6)**	**55**	**(45.8)**	**99**	**(46.7)**
Constipation	5	(14.7)	29	(13.6)	14	(11.7)	28	(13.2)
Diarrhoea	4	(11.8)	23	(10.7)	13	(10.8)	26	(12.3)
Digestive gas symptoms	3	(8.8)	8	(3.7)	2	(1.7)	1	(0.5)
Dyspepsia	2	(5.9)	11	(5.1)	4	(3.3)	12	(5.7)
Gastritis	2	(5.9)	4	(1.9)	2	(1.7)	4	(1.9)
Heartburn	2	(5.9)	9	(4.2)	5	(4.2)	11	(5.2)
Nausea	7	(20.6)	27	(12.6)	14	(11.7)	24	(11.3)
Oral candidiasis	3	(8.8)	6	(2.8)	4	(3.3)	1	(0.5)
Vomiting	1	(2.9)	14	(6.5)	7	(5.8)	16	(7.5)
Eyes, ears, nose and throat	**7**	**(20.6)**	**17**	**(7.9)**	**16**	**(13.3)**	**24**	**(11.3)**
Epistaxis	2	(5.9)	1	(0.5)	4	(3.3)	4	(1.9)
Pharyngitis	2	(5.9)	5	(2.3)	4	(3.3)	4	(1.9)
Hemic and lymphatic system	**5**	**(14.7)**	**27**	**(12.6)**	**13**	**(10.8)**	**23**	**(10.8)**
Anaemia	1	(2.9)	8	(3.7)	5	(4.2)	10	(4.7)
Febrile neutropenia	2	(5.9)	13	(6.1)	9	(7.5)	8	(3.8)
Neutropenia	4	(11.8)	6	(2.8)	2	(1.7)	13	(6.1)
Metabolism and nutrition	**4**	**(11.8)**	**41**	**(19.2)**	**20**	**(16.7)**	**43**	**(20.3)**
Anorexia	0	(0.0)	26	(12.1)	7	(5.8)	23	(10.8)
Appetite change	2	(5.9)	7	(3.3)	1	(0.8)	5	(2.4)
Weight loss	1	(2.9)	16	(7.5)	7	(5.8)	12	(5.7)
Musculoskeletal system	**2**	**(5.9)**	**13**	**(6.1)**	**12**	**(10.0)**	**20**	**(9.4)**
Muscular weakness	1	(2.9)	6	(2.8)	7	(5.8)	6	(2.8)
Nervous system	**6**	**(17.6)**	**37**	**(17.3)**	**16**	**(13.3)**	**36**	**(17.0)**
Headache	3	(8.8)	18	(8.4)	9	(7.5)	22	(10.4)
Insomnia	2	(5.9)	4	(1.9)	6	(5.0)	10	(4.7)
Respiratory system	**5**	**(14.7)**	**47**	**(22.0)**	**22**	**(18.3)**	**35**	**(16.5)**
Hiccups	3	(8.8)	26	(12.1)	19	(15.8)	19	(9.0)
Pneumonia	2	(5.9)	4	(1.9)	1	(0.8)	2	(0.9)
Skin and skin appendages	**4**	**(11.8)**	**22**	**(10.3)**	**9**	**(7.5)**	**7**	**(3.3)**
Rash	3	(8.8)	3	(1.4)	2	(1.7)	1	(0.5)

Aprepitant regimens
375 mg aprepitant 375 mg P.O. on Day 1 and 250 mg P.O. once daily on Days 2 to 5
125 mg aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 to 5
40 mg aprepitant 40 mg P.O. on Day 1 and 25 mg P.O. once daily on Days 2 to 5
Standard Therapy: ondansetron 32 mg IV and dexamethasone 20 mg P.O. on Day 1 and dexamethasone 8 mg P.O. once daily on Days 2 to 5

Additionally, a 4-week, multiple-dose safety study with aprepitant 375 mg was performed in healthy volunteers. No clinically important adverse experiences were reported.

Safety oral aprepitant

Since fosaprepitant is rapidly converted in aprepitant with similar off-peak plasma concentration and since there is no specific adverse event occurring following the infusion of fosaprepitant, the overall

safety profile of the treatment fosaprepitant/aprepitant could also be based on the safety information of aprepitant.

Frequently reported adverse reactions that were more common in the aprepitant treatment group were asthenia/fatigue and hiccups. These were also among the most frequently reported drug-related adverse experiences.
Other frequently reported adverse reactions that were slightly more common with aprepitant treatment included dizziness, diarrhoea, and cough. Constipation, headache, and anorexia were frequently reported as drug-related adverse experiences and were also more common in the aprepitant treatment group.

- Serious adverse event/deaths/other significant events

Serious adverse experiences of dehydration and respiratory insufficiency were frequent with aprepitant treatment during Cycle 1, but not during the Multiple-Cycle extension. The pre-specified adverse reactions, selected to reflect potential chemotherapy-induced haematologic toxicity, potential corticosteroid induced-toxicity and also toxicity potentially related to chemotherapy and/or corticosteroids, were generally similar in frequency between the treatment groups.

- Laboratory findings

Laboratory adverse reactions were generally similar in frequency between the treatment groups except for elevated alkaline phosphatase and increases aspartate aminotransferase that were both slightly more common in the aprepitant treatment group.

- Safety in special populations

Since fosaprepitant 115 mg on Day 1 followed by oral aprepitant on Days 2 and 3 provide a comparable efficacy and safety profile than the 3-day oral regimen in patients at risk for CINV receiving either HEC or MEC, the following information is based on the oral aprepitant.

No dose adjustment is necessary based on gender, age, or race. Neither fosaprepitant nor aprepitant have been evaluated in patients below 18 years of age.

Additionally, no dose adjustment is necessary for patients with renal insufficiency or for patients with end state renal disease undergoing haemodialysis or for patients with mild to moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency.

- Safety related to drug-drug interactions and other interactions

Drug-drug interactions were derived from studies conducted with fosaprepitant and midazolam or diltiazem and drug-interaction studies with oral aprepitant. As a general recommendation:

  - Fosaprepitant must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these medicinal products, potentially causing serious or life-threatening reactions
  - Caution is advised when warfarin, acenocoumarol, tolbutamide, phenytoin or other medicinal products that are known to be metabolised by CYP2C9 are administered during this time period
  - Fosaprepitant or aprepitant does not seem to interact with the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin.

- Discontinuation due to adverse events

Very few patients discontinued fosaprepitant or aprepitant due to adverse events during the clinical studies.

- Post-marketing experience

From market introduction of aprepitant in March 2003 through September 2005, a total of 332 spontaneous reports from both healthcare professionals including regulatory agencies (312) and consumers (20) were identified. Eighty of the 312 reports identified were serious. Six of these reports described patients less than 18 years of age.

Aprepitant is generally well tolerated, in particular, considering the potential drug interactions already highlighted. It is noteworthy that the post-marketing surveillance of aprepitant has not resulted in reports clearly suggestive of clinically significant drug interactions.

- Discussion on clinical safety

The oral aprepitant programme, with plasma aprepitant exposures at or above the peak aprepitant levels anticipated after fosaprepitant, as well as the available database of fosaprepitant exposure, provide evidence that fosaprepitant is well tolerated.

Because hypersensitivity reactions with polysorbate 80 have been documented, the formulation proposed in this Application for marketing authorisation utilises a low concentration of polysorbate 80 that is less than that used in other marketed products. Using this polysorbate concentration (0.05%) in 123 healthy volunteers did not reveal a clear hypersensitivity reaction.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Local tolerability	- Follow-up in Protocol #130 (A Randomized, Double-Blind, Parallel-Group Study Conducted Under In-House Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy) with optional extension cycle for treatment with IVEMEND (fosaprepitant dimeglumine) - Routine pharmacovigilance - Non-clinical study designed in accordance with CPMP/SWP/2145/00 with the commercial formulation and clinically relevant dosage regimen of fosaprepitant to investigate the potential risk for injection site reactions from accidentally mis-injected drug (i.e., paravenous, intramuscular, and subcutaneous exposure)	- Warning/precaution under SPC section 4.4 - Listed as ADR under SPC section 4.8 - Information on local tolerability included under SPC section 4.9 (overdose) - Information on local tolerability included under SPC section 5.3 (pre-clinical safety)

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Hypersensitivity	- Evaluation of hypersensitivity within Protocol #130 (for aprepitant) with optional extension cycle for treatment with IVEMEND - Routine pharmacovigilance	- Contraindication in SPC section 4.3 (Hypersensitivity to the active substance, aprepitant, polysorbate 80 or any of the excipients)
Important potential risks		
Medication errors	- Routine pharmacovigilance monitoring	- Statements in SPC sections 4.2 (Posology and Method of administration), 4.4 (Special Warnings and Precautions, 6 (Pharmaceutical Particulars) and Package Leaflet
Drug interactions: reduction of efficacy of oral contraceptives	- The MAH will continue to monitor post marketing reports of drug interaction and describe them in the PSURs	- Statement in SPC section 4.4 (Special Warnings and Precautions), 4.5 (Drug Interactions) and Package Leaflet
Important missing information		
Use in pregnancy	- Routine pharmacovigilance monitoring in pregnant and lactating women	- Statement under SPC section 4.6 (Pregnancy and Lactation), 5.3 (pre-clinical safety data) and Package Leaflet
Use in patients less than 18 years of age	- Evaluation of PK/safety/efficacy in patients < 18 years of age for aprepitant - Routine pharmacovigilance monitoring in patients less than 18 years of age	- Statement under SPC section 4.2 (Posology and Method of Administration) and Package Leaflet
Events of special interest		
Hepatobiliary events, QTc interval prolongation, infection, SIADH, nervous system events, drug interactions	- Follow-up under routine pharmacovigilance and describe them in the PSURs	- Periodic reassessment whether product information needs to be modified

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC.

The documentation provided for the active substance fosaprepitant (prodrug of aprepitant) is comprehensive and well detailed.

The pharmaceutical development is adequate for this intravenous formulation and took into consideration properties such as hygroscopicity and thermal lability of the active substance.

The excipients are those typically used for parenteral formulation. Similarly, the packaging material is well documented and no incompatibility has been noticed.

The validation of the manufacturing process ensures consistency and reproducibility of the finished product.

The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf life.

Non-clinical pharmacology and toxicology

Non-clinical data are satisfactory and do not raise any concern. However, the remained issue is the need for a non clinical study investigating the potential risk for significant local intolerance due to accidentally miss-administered drug as outlined in EU-guideline CPMP/SWP/2145/00 for which the Applicant has agreed as Follow-Up Measure.

Efficacy

No confirmatory clinical efficacy studies have been conducted with fosaprepitant. Activity in monotherapy and in combination with dexamethasone on acute and delayed emesis has been demonstrated in exploratory studies. Overall from an efficacy perspective, the absence of confirmatory studies is found fully appropriate given the submitted data on pharmacokinetics, available data on the pharmacodynamics of aprepitant and the efficacy results of Phase III programme of oral aprepitant.

Safety

The safety profile as documented and reported raises no concerns. Mild injection site reactions have been documented as a common event. There is no report submitted with respect to extravasation. There is a potential for hypersensitivity reactions related to PS80, but no such reactions have been reported yet for the formulation proposed for marketing.

No clustering of adverse events in relation to expected peak concentrations was observed.

An adequately designed thorough QTc study with moxifloxacin as positive control was conducted. A single dose of aprepitant of 200 mg is not associated with a clinically meaningful prolongation of QT.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk/management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

User consultation

The Patient Information Leaflet (PIL) for IVEMEND (fosaprepitant) has not been tested in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC since the PIL IVEMEND is similar to the aprepitant PIL except for the dosage section. This was considered acceptable justification.

Risk-benefit assessment

At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide the necessary information as Follow-Up Measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

The local tolerance at injection sites will be investigated according to the Guideline CPMP/SWP/2145/00 in a non clinical study as Follow-Up Measure.

Fosaprepitant I.V. infused over 15 minutes is rapidly converted into aprepitant. Bioequivalence with respect to aprepitant AUC between 115 mg fosaprepitant and 125 mg aprepitant has been demonstrated. Due to this equivalent exposure, efficacy of the regimen containing intravenous fosaprepitant on Day 1 is expected to be comparable to that provided when aprepitant is administered

orally on Day 1. Although higher aprepitant peak levels are observed following fosaprepitant infusion as compared to the currently registered oral aprepitant formulation, additional efficacy is unlikely, since brainstem NK_1 receptors are already fully occupied with the 125 mg oral regimen. Additional higher oral doses administered in the Phase II programme, which generated peak aprepitant plasma levels similar to or exceeding those following fosaprepitant administration, were associated with similar efficacy as 125 mg orally. The efficacy profile of the early formulations of fosaprepitant is consistent with the findings from the oral aprepitant studies.

There are sufficient safety data to support the conclusion that there is acceptable tolerability with the higher aprepitant peak plasma levels that will occur with fosaprepitant relative to oral aprepitant administration, including similar or higher peak concentration in the Phase II CINV (multiple-day but less than 1 week, exposure) and Phase III depression (multiple-week exposure) programmes. These exposures to aprepitant were well tolerated with no important differences from the tolerability profile already described in the aprepitant current SPC. Furthermore, fosaprepitant (various formulations) was well tolerated following intravenous administration in ~700 individuals, 78 of whom received ≥ 115 mg with the proposed market formulation; there were no major local tolerability concerns with the marketed formulations.

From a clinical perspective, benefit-risk is considered favourable.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus/majority decision that the risk-benefit balance of IVEMEND in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and of nausea and vomiting associated with moderately emetogenic cancer chemotherapy was favourable and therefore recommended the granting of the marketing authorisation.