London, 24 June 2010

EMA/559664/2010

ASSESSMENT REPORT

FOR

Ivemend

International Nonproprietary Name:
fosaprepitant

Procedure No. EMEA/H/C/000743/X/006

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents **Page**

1. Background information on the procedure 3
1.1. Submission of the dossier 3
1.2. Information on paediatric requirements 3
1.3. Scientific advice 3
1.4. Steps taken for the assessment of the product 3
2. Scientific discussion 4
2.1. Introduction 4
2.2. Quality aspects 4
2.2.1. Introduction 4
2.2.2. Active substance 5
2.2.3. Finished Medicinal Product 6
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 9
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 10
2.3. Non-clinical aspects 10
2.3.1. Introduction 10
2.3.2. Toxicology 10
2.3.3. Other non-clinical studies 11
2.3.4. Ecotoxicity/environmental risk assessment 11
2.3.5. Discussion and conclusion on non-clinical aspects 12
2.4. Clinical aspects 13
2.4.1. Introduction 13
2.4.2. Pharmacokinetics 13
Study Design 15
Populations Studies 15
Objectives 15
Analytical Methods 15
Pharmacokinetic data analysis 16
Statistical methods 16
Discussion on Clinical Pharmacokinetics 17
2.4.3. Clinical efficacy 18
2.5. Discussion & Conclusion on Clinical Efficacy 24
2.5.1. Clinical safety 25
2.6. Discussion & Conclusion on Clinical Safety 31
2.7. Pharmacovigilance 31
2.7.1. Detailed description of the pharmacovigilance system 31
2.7.2. Risk management plan 31
2.7.3. Benefit-risk balance 36
2.7.4. Recommendation 37

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 30 October 2009 an extension application to the European Medicines Agency for Ivemend 150 mg powder for solution for infusion pursuant to Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II (point 2 indent iii).

The MAH also provided with this submission the results of an animal study on local tolerance which was a follow-up measure (FUM) to the initial marketing authorisation of Ivemend 115 mg.

1.2. Information on paediatric requirements

Not applicable

This application does not fall within the scope of Article 8 of the paediatric regulation (it does not correspond to a new indication, new pharmaceutical form or new route of administration), therefore no PIP decision is included in this submission.

1.3. Scientific advice

Formal scientific advice has, according to the applicant, not been given by CHMP. National advice has been given by Sweden and The Netherlands in February 2009.

The Rapporteur appointed by the CHMP was:

Rapporteur: **Tomas Salmonson**

1.4. Steps taken for the assessment of the product

- The application was received by the Agency on 30 October 2009.
- The procedure started on 18 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 February 2010.
- During the meeting on 18 March 2010, 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 18 March 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 April 2010.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 June 2010.
- During the meeting on 24 June 2010, 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 150 mg powder for solution for infusion on 24 June 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 June 2010.

2. Scientific discussion

2.1. Introduction

Nausea and vomiting are common complications of 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.

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK1) receptors used for the prevention of 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).

Fosaprepitant is a water soluble phosphoryl prodrug to aprepitant. Following intravenous administration, fosaprepitant is rapidly converted to aprepitant *in vivo* via ubiquitous phosphatases. The pharmacologic activity of fosaprepitant is attributed to aprepitant.

The 115 mg strength fosaprepitant formulation was licensed in 2008 as an intravenous alternative to aprepitant on Day 1. This line extension application refers to the use of a single dose of fosaprepitant of 150 mg as add-on to a corticosteroid and a 5-HT3 antagonist regimen as an alternative to the 3-day regimens for the indication of the prevention of CINV.

2.2. Quality aspects

2.2.1. Introduction

Merck Sharp & Dohme Ltd has applied for a Line extension of marketing authorisation through the centralised procedure for a new higher strength (compared to the already approved 115 mg), Ivemend 150 mg powder for solution for infusion.

The only difference between the 150 mg and the already approved 115 mg presentation is the amount of powder contained in the vial. The different strengths are filled from the same bulk. Consequently in most parts of the documentation reference is made to the documentation for the already approved lower strength.

Concerning the active substance no new assessment has been performed.

For the finished product, the information has been very similar to the assessment of the 115 mg strength of Ivemend and the differences between the 2 strengths have been highlighted.

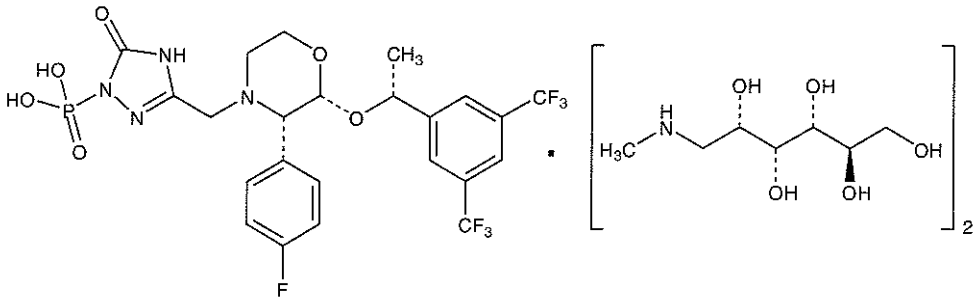
The finished product is packaged in a glass vial containing fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant.

2.2.2. Active substance

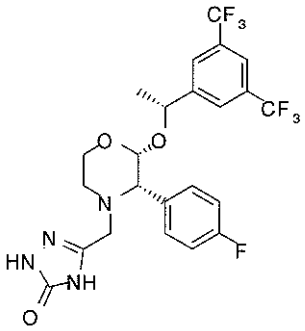
The active substance fosaprepitant dimeglumine is the water soluble pro-drug of already approved water-insoluble aprepitant (already marketed as a centralised product). This new product is intended to be an alternative to oral administration of aprepitant, to facilitate the nausea treatment. Fosaprepitant converts rapidly to aprepitant *in vivo* following intravenous administration.

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.

Structure of fosaprepitant dimeglumine (pro-drug)



Structure of aprepitant (drug)



2.2.2.1. Manufacture

The synthesis of fosaprepitant can be summarised in 3 main steps starting from aprepitant, including phosphorylation, debenzylation and hydrogenation prior to precipitation and isolation of the active substance.

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. Raw data with interpretations were provided.

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.

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.

2.2.2.2. Stability

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

Stability data were provided for three commercial batches (36 months) 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.

Based on the data provided (testing performed according to the established drug substance specification) it can be concluded that the as for the previous submission there is no sign of degradation. Data support a 3 years re-test period when the active substance is kept at -20°C.

2.2.3. Finished 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 150 mg of fosaprepitant free acid) in a lyophilised matrix.

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

The difference between the 150 mg presentation as compared to the already approved 115 mg presentation is only the fill volume of the vial.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.3.1. Pharmaceutical Development

Concerning the development work reference is made to the assessment of the already approved 115 mg strength.

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 formulation development focused on the following: limiting the degradation of fosaprepitant, preventing of precipitation of aprepitant as well as of insoluble salts of fosaprepitant and optimising the lyophilisation process. Reducing the exposure of fosaprepitant to environmental water has been focused on.

The following compendial excipients (PhEur) 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 possibly present aprepitant. The level of polysorbate has been optimised to solubilise aprepitant but 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 PhEur 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.

2.2.3.2. 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.

2.2.3.3. Manufacture of the product

The manufacturing process is the same as for the already approved 115 mg strength, only the fill volume differs. The key manufacturing steps that may impact product quality are compounding, lyophilization and stopper drying. Lyophilization and stopper drying remain unchanged from the 115mg product to the 150mg product. The compounding hold time specifications, process, and critical parameters also remain unchanged for the 150mg product although the manufacturing scale is slightly increased due to the increased fill volume.

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 sterilising 0.22 micron filter, filtration into pre-sterilised vials, lyophilisation and capping.

Adequate control of critical steps and intermediates has 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 150 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 validation applies to both the 115 and 150 mg presentations. Simulation of the aseptic process has been performed through media fill for both 150 and 115mg presentations.

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 PhEur requirements.

2.2.3.4. Product specification

The 150 mg strength is merely an extension of the 115mg strength, since the 150 mg presentation uses the same bulk solution as the 115 mg presentation with the only difference being the amount of solution filled into each vial.
Thus, the specifications for the 150 mg presentation are the same as those established previously for the approved 115 mg presentation. The only difference in the specification for the 115 mg versus the 150 mg presentation is that the acceptance criterion for "bacterial endotoxins" has been adjusted to account for the additional mass in the vial.

The release and shelf life specification for IVEMEND 150 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 five pilot scale batches kept in the commercial packaging has showed that all batches remain within the proposed specification.

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 PhEur requirements.

2.2.3.5. Stability of the product

Stability Summary and Conclusion
Stability data for the 150 mg presentation was already provided in the dossier for the 115 mg presentation as supportive data.

In the present submission data from the formal stability studies in terms of up to 24 months of long-term data at 5°C/ambient humidity (one batch of 24 months and four batches of 9 months) and 6 months accelerated data at 25°C/60%RH from the formal Stability Studies. The batches are of commercial scale and have been manufactured with the current process.

Testing is performed according to the proposed specification and in addition reconstitution time is checked.

Post-approval Stability Protocol and Stability Commitment
The post-approval stability program is accounted for in general words, where it is stated that the program will continue and that stability studies will be carried out for validation batches and/or early commercial batches (validation batches) and that additional batches will be placed on the program each year.

Stability data
From data provided it may be concluded that at long-term storage condition there is no significant degradation as judged by assay values and the level of aprepitant. At accelerated condition there is an acceptable increase in aprepitant level. The product is stable for 24 months when stored refrigerated (2-8°C).

Statistical analyses are provided. Comparisons are made to the 115 mg presentation.

Based on the stability data, the shelf-life when stored under the conditions detailed in the SPC can be supported.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The product in this application is a line extension, a new higher strength 150 mg as compared to the already approved 115 mg strength.

Active substance
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.

Drug Product
The only difference between the 150 mg and the already approved 115 mg presentation is the amount of powder contained in the vial. The different strengths are filled from the same bulk.

Even though the provided stability data as well as data submitted for the 115 mg presentation gave assurance of the stability of the product, additional stability data collected since the submission of the application, were requested. Accordingly, updated stability data have been provided for the five batches that were included in the original submission. 24 months data from long term storage at 5°C/ambient humidity are available for one batch and 12 months for the other four batches. There is no sign of degradation. The product is stable for 24 months when stored refrigerated (2-8°C).

In summary, 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product Ivemend 150 mg powder for solution form infusion is considered satisfactory when used with the conditions defined in the SPC. This product is a line extension from the existing Ivemend 115 mg powder for solution for infusion, the only difference between the two products is the fill volume of the vial.

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.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical evaluation focused on the relevance of the previous toxicity studies conducted with aprepitant/fosaprepitant for the exposure with the increased dose of fosaprepitant. No new non-clinical pharmacology or pharmacokinetic data were submitted for fosaprepitant.

The potential of the excipient polysorbate 80 to interfere with P-glycoprotein was evaluated separately. An environmental risk assessment was furthermore requested for this application.

In addition, the results of an animal study on local tolerability were submitted with this application which was a follow-up measure (FUM) to the initial marketing authorisation of Ivemend 115 mg. A statement of compliance with GLP was provided for this study (TT#08-7590).

2.3.2. Toxicology

The applicant,stated that the full toxicity profiles of fosaprepitant or aprepitant have not been investigated due to limited exposure multiples. For aprepitant, significant exposure multiples (C_{max} and AUC) have been reached only in one species (dog, sufficient exposure margin to target organs of prostate, testis, ovaries, thymus). In the low-exposed rats, receiving aprepitant for 5 weeks, target organs were liver and thyroid together with changes in clinical chemistry and hematology. For fosaprepitant, no multiples to AUC and only borderline multiples to C_{max} (dog/monkey) have been

investigated. The predominant toxicity observed following IV administered fosaprepitant was injection site reactions. The option to further increase exposure was not investigated in the different species, i.e. a second species for aprepitant and two species for fosaprepitant.

Local tolerance

The MAH has provided the results of a single-dose local tolerability study in rabbits (TT#08-7590) which was a follow-up measure of the initial marketing authorisation of Ivemend 115 mg. The potential risk for injection site reactions following accidental mis-administration of fosaprepitant was evaluated following single intravenous, intramuscular, paravenous, and subcutaneous doses to female and male New Zealand White rabbits. A total of 40 New Zealand White rabbits (20 females, 20 males) received 0.5 ml of a commercial formulation of fosaprepitant (1 mg/ml) either as an intravenous, intramuscular, paravenous or subcutaneous bolus injection in specific locations on the left side of the animals. Placebo control formulation was given by the same routes of administration on the animals' right side.

At interim necropsy on study day 2, the incidence and/or severity of histomorphologic changes observed at all fosaprepitant-treated injection sites were increased compared to placebo control. Initial acute inflammation was reported in the majority of animals independent of the route of administration (day 2). For certain routes of administration, very slight to moderate subacute inflammation (PV, IM) and very slight to moderate muscle degeneration and necrosis (IM) were evident at study termination (final necropsy on study day 8). How these reactions developed beyond day 8 was not followed, i.e. whether they resolved or further progressed were thus not investigated.

2.3.3. Other non-clinical studies

The MAH has evaluated the potential of the excipient polysorbate 80 to interfere with P-glycoprotein.

Polysorbate 80 (PS80) is a component of the fosaprepitant formulation for intravenous administration. The potential of PS80 to act as an inhibitor of P-glycoprotein (P-gp) was assessed *in vitro* in LLC-PK1 cell monolayers that stably express a human MDR1 cDNA; verapamil and quinidine were used as marker P-gp substrates. PS80 was found to be a weak inhibitor of human MDR1-mediated verapamil and quinidine transport, with apparent IC_{50} values of 66 ± 8 and 200 ± 30 µM, respectively. Under the conditions of these experiments, cyclosporin A (10 µM) nearly completely inhibited the P-gp-mediated transport of verapamil and quinidine. The fosaprepitant 150 mg formulation contains approximately 78 g of PS80. Thus, an injection of this product into the bloodstream over a minute would result in 78 mg of PS80 distributing into approximately 5 liters of blood. This, in turn, would result in a peak PS80 concentration in blood of approximately 16 µg/ml or 12 µM (assuming a molecular weight for PS80 of 1,310 Da); this peak concentration would be expected to be much lower if the product is infused over a period of 15 min. Since the IC_{50} values for PS80 for the inhibition of P-gp mediated transport are considerably higher than the anticipated peak concentrations, it was considered unlikely that the amounts of PS80 in the fosaprepitant product will result in significant inhibition of P-gp *in vivo*.

2.3.4. Ecotoxicity/environmental risk assessment

The applicant has responded on the question raised in the primary assessment. A second question has now been raised. This is proposed to be solved as a Follow up measure.

The applicant provided an updated environmental risk assessment (ERA) for the current line extension application of the product Ivemend.

The applicant`s approach to conduct the ERA with the active substance aprepitant is supported because fosaprepitant is a pro-drug.

A value for the n- octanol/water partition coefficient (logKow 4.8) is included in the updated ERA. The value exceeds the action limit (log Kow >4.5) for a step- wise screening procedure on persistence, bioaccumulation an toxicity according to the requirements of guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). But the value cannot be validated yet. Therefore the applicant is asked to submit the study report for the determination of the logKow. If the value of 4.8 is considered to be valid the applicant will be asked to provide a step-wise screening for persistence, bioaccumulation and toxicity.

The applicant included two approaches for the calculation of PECsurfacewater (PECsw) in the updated ERA.

The first approach is based on number of treated patients in the EU within 6 years (data submitted in module 1.8.2). From the data for the 6 years period it is acceptable to calculate the number of patients treated within one year. The number of patients is acceptable for an refinement of marketing penetration factor Fpen in Phase I of the ERA.

Moreover the applicant included treatment cycles into the PEC calculation resulting in a value for PECsurfacewater of 3.75x10-5 µg/L. This approach is not acceptable because the consideration of treatment cycles is not acceptable for a refinement of PECsw in Phase I assessment.

If only the number of treated patients is taken into consideration for calculation of PECsurfacewater will be 0.0135µg/L. This value exceeds the trigger value and therefore a Phase II assessment has to be provided.

The second approach for calculation of PECsurfacewater is based on sales forecast data. This is not acceptable for a refinement in Phase I assessment. It can only be taken into consideration in a Phase II assessment for further refinement of PECsurfacewater.

For a Phase II fate and effect assessment the applicant has only provided endpoints of aquatic effect studies in the updated ERA (Attachment A). This is not sufficient. The endpoint data cannot be validated and can therefore not be used for risk assessment. The applicant is asked to provide a Phase II fate and effect assessment on aprepitant according to the requirements of guideline EMEA/CHMP/SWP/4447/00. This also includes the study reports on the aquatic effect studies cited in Attachment A of the environmental risk assessment.

2.3.5. Discussion and conclusion on non-clinical aspects

Apart from the local tolerance study, no new non-clinical data have been provided with this application as extensive non-clinical studies were conducted to support registration of fosaprepitant 115 mg. In the non-clinical overview submitted with this application the MAH justified the relevance of the previous toxicity studies conducted with aprepitant/fosaprepitant for the exposure with an increased dose of fosaprepitant. Appropriate information such as the low exposure in animals limiting the value of the toxicity studies is given in the SPC 4.6 and 5.3. This was acceptable for the CHMP.

The results of the local tolerance study in rabbits demonstrate the potential risks associated with accidental mis-administration of fosaprepitant. The medical care professionals administering fosaprepitant should be aware of the undue local reactions reported in the rabbits of 'mis-administered' Ivemend. Therefore, a warning statement has been added in the SmPC section 4.4, and appropriate wording has been included in section 5.3.

Fosaprepitant 150 mg dose contains 78 mg PS80 (115 mg dose contains 60.4 mg PS80). The CHMP concurred with the MAH's conclusion this amount is unlikely to result in significant inhibition of P-gp *in vivo* and is below a level raising safety concerns.

A question regarding the company's approach for the ERA has been raised as an other concern and should be addressed as a follow up measure.

In conclusion, the proposed single fosaprepitant 150 mg dose to replace the three-day regimen with (fos)aprepitant, does not raise concerns from a nonclinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The already approved fosaprepitant 115 mg strength was licensed as an intravenous alternative to oral aprepitant 125 mg to be taken on day 1 prior to start of the chemotherapy treatment. The present line extension refers to the use of a single dose of fosaprepitant 150 mg as add-on to a corticosteroid and a 5-HT3 antagonist regimen as an alternative to the 3-day regimens. The underlying rationale is that the fosaprepitant 150 mg regimen will provide comparable efficacy and safety profiles as the 3-day oral aprepitant regimen evaluated in previous highly and moderately emetogenic chemotherapy (HEC, MEC) trials.

In support of this application, the MAH submitted the results of a Phase 3 non-inferiority trial between the single-dose fosaprepitant 150 mg regimen and the approved 3-day oral aprepitant regimen (P017L1). Furthermore, an open-label Phase 1 study to evaluate the effect of a single 150 mg IV dose of fosaprepitant (MK-0517) on the pharmacokinetics of oral dexamethasone and oral midazolam has been provided (P018L1).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Following intravenous administration, fosaprepitant is rapidly (within 30 minutes) converted to aprepitant. The aprepitant pharmacokinetic profile after a single 150 mg fosaprepitant infusion and the CINV 3-day aprepitant 125/80/80 mg treatment regimen has been evaluated by means of a cross-study comparison.

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4 when administered as a 3-day antiemetic regimen for CINV (125/80/80 mg). The involvement of CYP3A4 in the oxidative metabolism of dexamethasone in human liver microsomes is well established. Systemic exposure to aprepitant has been shown to inhibit CYP3A4 following single-dose administration of aprepitant and of fosaprepitant. In previous studies, this led to dose-dependent increases in midazolam or dexamethasone exposures, as each of these compounds are substrates for CYP3A4. With this application an interaction study evaluating the influence of fosaprepitant 150 mg single dose on dexamethasone exposure Days 1, 2 and 3 and midazolam exposure Days 1 and 4 after fosaprepitant administration was submitted (study P018L1).

2.4.2.1. Pharmacokinetics profile of aprepitant

The MAH has provided a cross-study comparison of the aprepitant pharmacokinetic profile after a single 150 mg fosaprepitant infusion (study P165) and the CINV 3-day aprepitant 125/80/80 mg

treatment (study P067). A visual comparison of the aprepitant plasma concentration-time profile for both regimens is shown in Figure 1.

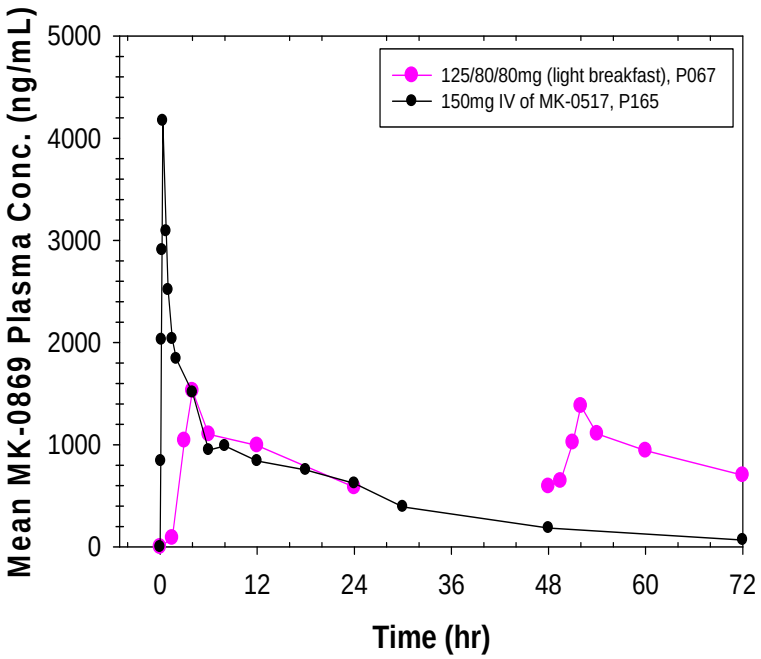


Figure 1. Mean aprepitant plasma concentrations (ng/ml) versus time from single-dose intravenous (IV) 150 mg fosaprepitant and from oral aprepitant 125/80/80 mg regimen. [Note: The above plot for the oral 125/80/80 mg aprepitant regimen does not show Day 2 (24 to 48 hrs) because aprepitant exposure was not measured at that time.]

Aprepitant exposure is higher during the first 4 hours after administration of fosaprepitant 150 mg than after administration of aprepitant 125 mg orally, with about 2.5 to 3-fold higher C_{max}. The concentration-time profiles are thereafter similar until the second dose of the aprepitant CINV regimen is administered, where after the aprepitant concentrations are lower for the fosaprepitant single-dose regimen.

Special populations

The applicant justified the absence of specific studies in special population (hepatic insufficiency and renal insufficiency) by stating that the studies previously conducted within the oral aprepitant development program adequately cover the use of 150 mg fosaprepitant in these populations given that the aprepitant exposure is comparable. The effect of intrinsic factors on aprepitant pharmacokinetics is expected to be similar for the fosaprepitant 150 mg dose and the aprepitant CINV regimen. Hence, the lack of studies evaluating the pharmacokinetics of fosaprepitant in special populations was considered acceptable by the CHMP.

2.4.2.2. Pharmacokinetic Interaction Study

P018L1: An Open-Label, 2-Part, Randomized, 2-Period, Crossover, Single-Center Study to Evaluate the Effect of a Single 150-mg Intravenous Dose of Fosaprepitant Dimeglumine (MK-0517) on the Pharmacokinetics of Oral Dexamethasone in Part 1, and on the Pharmacokinetics of Oral Midazolam in Part 2, in Healthy Young Adult Subjects

Methods

Study Design

This was an open-label, 2-part, randomized, 2-period, crossover, single-center study consisting of 4 study drug treatments (A and B in Part 1; C and D in Part 2):

Treatment A: A single 8 mg oral daily dose of dexamethasone alone on Days 1, 2, and 3.

Treatment B: A single 8 mg oral daily dose of dexamethasone on Days 1, 2, and 3 co-administered with a single 150 mg intravenous dose of fosaprepitant dimeglumine infused over 30 minutes on Day 1.

Treatment C: A single 2 mg oral daily dose of midazolam alone on Days 1 and 4.

Treatment D: A single 2 mg oral daily dose of midazolam on Days 1 and 4 co-administered with a single 150 mg intravenous dose of fosaprepitant dimeglumine infused over 30 minutes on Day 1.

Populations Studies

Twelve healthy young adult subjects were planned to participate in Part 1 and 10 subjects in Part B of the study. Each subject participated in only Part 1 (Dexamethasone Interaction) or Part 2 (Midazolam Interaction) of the study. There was a washout of at least 14 days between each treatment period. Subjects were administered study drug in the fasted state.

Objectives

Primary:

To evaluate the effect of a single 150 mg intravenous dose of fosaprepitant on CYP3A4 activity in healthy subjects as measured by the pharmacokinetics of dexamethasone and midazolam, respectively, following oral administration.

Secondary:

To assess the safety and tolerability of a single 8 mg oral daily dose of dexamethasone and single 2 mg oral daily dose of midazolam, respectively, co-administered with a single 150 mg IV dose of fosaprepitant infused over 30 minutes.

Analytical Methods

Plasma samples collected following administration of dexamethasone in both treatment periods in **Part 1** of the study were analyzed for dexamethasone concentrations. The analytical method involved liquid-liquid extraction for analyte isolation followed by hydrophilic interaction liquid chromatography coupled with tandem mass spectrometric detection. Satisfactory accuracy and precision was shown for lower limit of quantification, low, medium and high QC sample concentrations. Linearity was demonstrated within the calibration range 0.500 to 500 ng/ml. Dilution integrity was demonstrated. Stability in plasma was demonstrated for 307 days at -20°C, exceeding the duration of sample storage.

Plasma samples collected following administration of midazolam in both treatment periods in **Part 2** of the study were analyzed for midazolam concentrations. The analytical method involved liquid-liquid extraction for analyte isolation followed by hydrophilic interaction liquid chromatography coupled with tandem mass spectrometric detection. Satisfactory accuracy and precision was shown for lower limit of

quantification, low, medium and high QC sample concentrations. Linearity was demonstrated within the calibration range 0.100 to 100 ng/ml. Stability in plasma was demonstrated for 364 days at -20°C, exceeding the duration of sample storage.

Pharmacokinetic data analysis

Pharmacokinetic parameters $AUC_{0\text{-}24hr}$ and C_{max} for oral dexamethasone and oral midazolam were obtained by non-compartmental methods.

Statistical methods

The effect of a single dose of 150 mg fosaprepitant on the dexamethasone and midazolam pharmacokinetic parameters ($AUC_{0\text{-}24hr}$ and C_{max}) was evaluated using a linear mixed effects model appropriate for a 2-period, crossover design with fixed effects terms of sequence, period, day, treatment and treatment by day interaction and a random effect term of subject within sequence. Log transformation on $AUC_{0\text{-}24hr}$ and C_{max} was applied. A two-sided 90% confidence interval for the true mean difference in $AUC_{0\text{-}24hr}$ in the log scale was calculated. These confidence limits were then exponentiated to obtain a confidence interval for the true geometric mean ratio (GMR) for $AUC_{0\text{-}24hr}$. C_{max} was analyzed in a similar fashion. Summary statistics (minimum, maximum, and median) were provided for T_{max}. Harmonic mean and pseudo standard deviation were provided for apparent terminal $t_{1/2}$.

Results

Twenty-three (23) subjects (10 males and 3 females in Part 1; 6 males and 4 females in Part 2) were enrolled into the study. Of these 21 completed the study as planned (11 subjects in Part 1; 10 subjects in Part 2) while 2 subjects (AN 0002 and AN 0003) discontinued the study prematurely. Female subject AN 0002 withdrew consent and discontinued from Part 1 of the study for personal reasons. Male subject AN 0003 was discontinued from Part 1 of the study due to serious clinical adverse experiences (pneumonia and pulmonary embolism) which were considered unrelated to the study drug by the investigator.

The subject disposition of study P018L1 is given in the table below:

Table 1. Subject disposition in study P018L1

	Part 1 of Study	**Part 2 of Study**	**Total**
RANDOMIZED	13	10	23
Male (age range in yrs)	10 (18 to 45)	6 (18 to 44)	16 (18 to 45)
Female (age range in yrs)	3 (22 to 30)	4 (23 to 43)	7 (22 to 43)
COMPLETED:	11	10	21
DISCONTINUED:	2	0	2
Clinical adverse experience	1 (AN 0003)	0	1
Laboratory adverse experience	0	0	0
Other	1 (AN 0002)	0	1

The pharmacokinetic results for study completers are shown in Table 3.

Table 2. Statistical Comparison of Pharmacokinetic Parameters of study P018L1

Part 1 of the Study (N=11) – Dexamethasone Interaction					
Pharmaco-kinetic Parameter	Day	Geometric Mean† (Dexamethasone + MK-0517) (Treatment B)	Geometric Mean† (Dexamethasone Alone) (Treatment A)	GMR (Dexamethasone + MK-0517 / Dexamethasone Alone)	90% CI for GMR
AUC_{0-24hr} (ng•hr/mL)	1	732.6	363.8	2.01	(1.84, 2.20)
	2	528.2	283.3	1.86	(1.71, 2.03)
	3	298.0	252.5	1.18	(1.08, 1.29)
C_{max} (ng/mL)	1	87.53	70.36	1.24	(1.09, 1.42)
	2	82.28	62.99	1.31	(1.14, 1.49)
	3	67.11	57.01	1.18	(1.03, 1.34)
Part 2 of the Study (N=10) – Midazolam Interaction					
Pharmaco-kinetic Parameter	Day	Geometric Mean† (Midazolam + MK-0517) (Treatment D)	Geometric Mean† (Midazolam Alone) (Treatment C)	GMR (Midazolam + MK-0517/ Midazolam Alone)	90% Confidence Interval for GMR
$AUC_{0-\infty}$ (ng•hr/mL)	1	49.4	28.0	1.77	(1.52, 2.05)
	4	27.7	27.2	1.02	(0.88, 1.18)
C_{max} (ng/mL)	1	9.73	8.33	1.17	(0.98, 1.38)
	4	8.42	8.82	0.96	(0.81, 1.13)
† Geometric mean computed from a linear mixed-effects model performed on the natural-log transformed values.					

Dexametasone AUC was increased by 101, 86 and 18% on Days 1, 2 and 3, respectively. The corresponding C_{max} values were 24, 31 and 18%. Dexamethasone half-life was prolonged from 3.6 and 3.0 h for dexamethasone alone to 5.7 and 4.0 h, respectively, on days 1 and 2 after administration with fosaprepitant.

Midazolam AUC increased by 77% and C_{max} by 17% on Day 1. There was no effect on midazolam AUC or C_{max} on Day 4. Midazolam half-life was prolonged from 4.6 for midazolam alone to 6.2 h on day 1 after administration with fosaprepitant.

Discussion on Clinical Pharmacokinetics

Given the intravenous administration (avoiding inhibition of intestinal CYP3A4) and the shorter duration of administration, a lower CYP3A4 inhibitory potential for fosaprepitant 150 mg single dose than for the aprepitant 3-day CINV regimen was expected. This was explored in the interaction study P018L1 which demonstrated an overall somewhat lower effect of fosaprepitant 150 mg single dose on orally administered CYP3A4 substrates than the 3-day oral aprepitant regimen. The effect on Day 1 is fairly similar for the two regimens, however, the inhibitory effect by fosaprepitant 150 mg is of a shorter duration. The effect of fosaprepitant 150 mg on dexamethasone Day 1 (101% increase) was similar to that observed for aprepitant 125 mg (120% increase). For midazolam, the effect of fosaprepitant 150 mg on day 1 (77% increase) was somewhat smaller than that for aprepitant 125 mg (130% increase).

The dexamethasone data showed that an inhibitory effect is maintained on Day 2 (86% increase), but has essentially disappeared on Day 3 (18% increase). No effect on midazolam was seen on Day 4.

These data support the proposed dexamethasone dose on Days 1 and 2 (about 50% reduction) and the unchanged dose on Days 3 and 4.

Based on the conducted midazolam interaction study, the applicant suggested that the midazolam Day 4 data support the conclusion that a single fosaprepitant 150 mg dose does not have a clinically relevant inducing effect on CYP3A4. In response to questions raised during the assessment, the applicant discussed if there is a risk for clinically relevant induction of CYP3A4 at later time points than Day 4. The data suggest that 150 mg fosaprepitant should result in similar or less induction than for the aprepitant 125/80/80 mg CINV regimen and this has been reflected appropriately in section 4.5 of the SPC.

Because of the pharmacokinetic findings within Part 1 of the study, the dexamethasone oral dosing regimen in fosaprepitant Protocol 017 (P017L1) in the fosaprepitant 150 mg arm of the study was established as 12 mg q.d. on Day 1, 8 mg q.d. on Day 2, and 8 mg b.i.d. (i.e., every 12 hours) on Days 3 and 4, i.e. a dose reduction by 50% on days 1 and 2 and the normal dose on days 3 and 4, as compared to the oral aprepitant arm wherein the dexamethasone oral dosing regimen was established as 12 mg q.d. on Day 1 and 8 mg q.d. on Days 2 to 4, where the dexamethasone dose is reduced by 50% days 1-4.

The CYP3A4 inhibition caused by oral aprepitant is a mixture of inhibition of intestinal and hepatic CYP3A4, while the CYP3A4 inhibition caused by fosaprepitant can be attributed to hepatic CYP3A4 inhibition alone. In the response to questions, the applicant has discussed the available data on inhibition of hepatic CYP3A4 of aprepitant and fosaprepitant. The effect of aprepitant 125 mg on hepatic CYP3A4 was evaluated after administration of intravenously administered midazolam, and resulted in an increase in midazolam AUC of about 50%. The effect of fosaprepitant on IV midazolam has not been evaluated. The effect of fosaprepitant 150 mg on oral midazolam is larger (77%) than that of aprepitant on IV midazolam. This may be explained by an effect also on the first pass metabolism of orally administered midazolam. The effect on midazolam half-life for fosaprepitant and aprepitant was similar (about 27% increase) suggesting a similar effect on hepatic CYP3A4.

There are no data on CYP2C9 substrates but a single fosaprepitant 150 mg dose is expected to cause no greater induction of CYP2C9 or glucuronidation than the aprepitant 125/80/80 mg CINV regimen and the absence of data was therefore acceptable for the CHMP.

2.4.3. Clinical efficacy

2.4.3.1. Dose response study(ies)

The 150 mg fosaprepitant dose was selected based on pharmacokinetic data from previously conducted studies investigating the pharmacokinetics of various doses and administration regimens for IV fosaprepitant and the aprepitant-NK1 receptor occupancy relationship established for aprepitant after oral administration. Based on observed plasma aprepitant levels obtained on Days 2-4 following a single 15 or 30 minute infusion of fosaprepitant, CNS NK1 receptor occupancy levels were predicted to remain greater than 90% through at least Day 3 following a single 150 mg IV fosaprepitant dose administered over 20-30 minutes and greater than or equal to approximately 80% through at least Day 4. Protocol P017L1 was, therefore, designed to test the hypothesis that receptor occupancy levels of this degree would be sufficient to confer similar (i.e., non-inferior) clinical efficacy compared to the approved 3-day oral regimen.

2.4.3.2. Main study

P017L1: Randomized, Double-Blind, Active-Controlled, Parallel-Group Study for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Cisplatin Chemotherapy

Methods

Study Participants

Main Inclusion Criteria

- Patient is female or male, and is >18 years of age.
- Patient is scheduled to receive his/her first course of cisplatin chemotherapy for a documented solid malignancy at a dose of ≥70 mg/m^2.
- Patient is able to understand study procedures and agrees to participate in the study by giving written informed consent.

Main Exclusion Criteria

- Patient is to receive multiple-day chemotherapy with cisplatin in a single cycle.
- Patient is to receive chemotherapy of moderate or high emetogenicity (per Hesketh Classification of Emetogenic Chemotherapy Agents) during the 6 days prior to the cisplatin infusion and/or during the 6 days following cisplatin infusion.
- Chemotherapy agents with a classification of moderate or above can be given on the same day as cisplatin, and should be administered following the cisplatin infusion.
- Paclitaxel, docetaxel and pemetrexed must be given on the same day as cisplatin and prior to cisplatin.

Treatments

Fosaprepitant Regimen:	fosaprepitant (150 mg IV on Day 1) in combination with ondansetron (32 mg IV Day 1) and dexamethasone (12 mg on Day 1, 8 mg on Day 2, and 16 mg on Days 3 and 4).
Aprepitant regimen:	aprepitant (125 mg PO on Day 1 and 80 mg on Days 2 and 3) in combination with ondansetron (32 mg IV on Day 1) and dexamethasone (12 mg on Day 1, 8 mg on Days 2 and 3, and 4).

Objectives

The aim of the study was to investigate whether a single "high dose" of fosaprepitant IV is non-inferior to the licensed, oral aprepitant regimen administered over 3 days as add-on to a high-dosed 5-HT3 antagonist based standard regimen.

Outcomes/endpoints

Primary

1. Complete Response - Overall (no vomiting and no use of rescue therapy in the 120 hours following initiation of cisplatin).
2. Infusion-site reactions (thrombophlebitis, severe pain, severe erythema, severe induration)

Secondary

1. Complete Response - Delayed Phase (no vomiting and no use of rescue therapy 25 to 120 hours following initiation of cisplatin).
2. No Vomiting - Overall (in the 120 hours following initiation of cisplatin).

In addition, the study evaluated a number of exploratory endpoints, e.g.

- Complete Respone – Acute (0 to 24 hours following initiation of cisplatin)
- No Impact on Daily Life (FLIE total score >108) – Overall
- Time to first vomiting/retching episode- Overall (0 to 120 hours following initiation of cisplatin);
- Complete Protection – Overall (no vomiting, no use of rescue therapy and maximum nausea VAS <25 mm; evaluated 0 to 120 hours following initiation of cisplatin))

Sample size

It was estimated that to address the primary hypothesis, a total of 2,292 patients will need to be enrolled to yield approximately 2,226 evaluable patients. It was anticipated that 1,113 evaluable patients per regimen, assuming a 2-sided 5% significance level for testing the primary efficacy hypothesis and an expected response rate of 67.7% in each treatment regimen, would yield 90% power to declare non-inferiority for the single-dose fosaprepitant dimeglumine regimen, using a non-inferiority margin of 7 percentage points.

The sample size calculation considered a planned futility analysis which is accompanied by a slight loss of power.

Randomisation

Eligible patients who met the inclusion criteria and were randomized to treatment based on a computer generated allocation schedule.

Blinding (masking)

Investigators, study nurses and patients remained blinded to the study medication. An allocation schedule and blinded supplies were provided by the sponsor. Open-label fosaprepitant vials were supplied to an unblinded pharmacist or designee who prepared the IV infusion bags containing fosaprepitant or normal saline solution. Full details of the procedure for the unblinded pharmacist were contained in a separate Standard Operating Procedure (SOP). Unblinding envelopes were provided for emergency unblinding in case of serious adverse experiences or medical emergencies when knowledge of the treatment group for a given patient may be necessary.

Statistical methods

The pre-defined non-inferiority margin was -7%. The two pivotal registration studies for aprepitant, studies P051 and P054, were used to define this margin.

All efficacy analyses were based on the Full Analysis Set (FAS) patient population. The FAS population included patients who received at least one dose of study therapy, received cisplatin chemotherapy, and had at least one post-treatment efficacy assessment. The Per Protocol (PP) patient population excluded patients with important deviations from the protocol that might have substantially affected the results of the efficacy analyses.

Results

Subject disposition:

Table 3. Subject disposition in study P017L1

	Fosaprepitant Regimen n	(%)	Aprepitant Regimen n	(%)	Total n	(%)
SCREENING FAILURES:					163	
RANDOMIZED:	1,147		1,175		2,322	
Male (age range)	722 (19-83)	62.9	748 (19-82)	63.7	1470 (19-83)	63.3
Female (age range)	425 (20-86)	37.1	427 (20-79)	36.3	852 (20-86)	36.7
COMPLETED:	1,080	94.2	1,094	93.1	2,174	93.6
DISCONTINUED:	67	5.8	81	6.9	148	6.4
Clinical adverse experience	32	2.8	36	3.1	68	2.9
Laboratory adverse experience	0	0.0	0	0.0	0	0.0
Other	35	3.1	45	3.8	80	3.4

Recruitment

The study initiation (FPI) was on 13-Feb-2008 and completed on 29-Jun-2009 (LPO). Patients were entered at 149 study sites worldwide. Enrolment at each study center ranged from 1 to 80 patients.

Baseline data

Table 4. Baseline Patient Demographic and Characteristics by Treatment Group

	Fosaprepitant Regimen n	(%)	Aprepitant Regimen n	(%)	Total n	(%)
Patients in population	1,147		1,175		2,322	
Gender						
Male	722	(62.9)	748	(63.7)	1,470	(63.3)
Female	425	(37.1)	427	(36.3)	852	(36.7
Age (YEARS)						
< 55	491	(42.8)	475	(40.4)	966	(41.6)
≥ 55	656	(57.2)	700	(59.6)	1,356	(58.4)
17 and under	0	(0.0)	0	(0.0)	0	(0.0)
18 to 34	67	(5.8)	68	(5.8)	135	(5.8)
35 to 54	424	(37.0)	407	(34.6)	831	(35.8)
55 to 64	402	(35.0)	418	(35.6)	820	(35.3)
65 to 74	226	(19.7)	246	(20.9)	472	(20.3)
Over 74	28	(2.4)	36	(3.1)	64	(2.8)
Mean	55.2		55.9		55.6	
SD	11.9		12.0		12.0	
Median	56.0		57.0		57.0	
Range	19 to 86		19 to 82		19 to 86	
Race						
AMERICAN INDIAN OR ALASKA NATIVE	32	(2.8)	33	(2.8)	65	(2.8)
ASIAN	296	(25.8)	306	(26.0)	602	(25.9)
BLACK OR AFRICAN AMERICAN	21	(1.8)	22	(1.9)	43	(1.9)
MULTI-RACIAL	149	(13.0)	157	(13.4)	306	(13.2)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	(0.1)	2	(0.2)	3	(0.1)

	Fosaprepitant Regimen n	(%)	Aprepitant Regimen n	(%)	Total n	(%)
WHITE	648	(56.5)	655	(55.7)	1,303	(56.1)
Ethnicity						
HISPANIC OR LATINO	370	(32.3)	393	(33.4)	763	(32.9)
NOT HISPANIC OR LATINO	777	(67.7)	782	(66.6)	1,559	(67.1)

Numbers analysed

Of the 2,322 patients randomized, 2,247 were included in the FAS (3.2% exclusion from total randomized population). Thirty-seven patients of the aprepitant regimen and 38 patients on the fosaprepitant regimen were excluded. Reasons for exclusion included patients not receiving study drug, patients not having a post-baseline efficacy assessment or patients not receiving cisplatin chemotherapy. Of the 2,247 patients included in the FAS population 2,203 (2.0% exclusion from FAS) patients were included in the PP population. The reasons for exclusion included violation of inclusion/exclusion criteria, patients not receiving highly emetogentic chemotherapy level cisplatin, patients taking prohibited medication or patients not taking all required study medication.

Outcomes and estimation

Efficacy outcome measure:

Table 5. Number (%) of Patients with Complete Response by Phase and Treatment Group with the Difference Between Treatment Groups - Full Analysis Set Patient Population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	795/1106	71.9 (69.1, 74.5)	820/1134	72.3 (69.6, 74.9)	-0.4 (-4.1, 3.3)
Acute Phase	963/1082	89.0 (87.0, 90.8)	974/1107	88.0 (85.9, 89.8)	1.1 (-1.6, 3.8)
Delayed Phase	822/1106	74.3 (71.6, 76.9)	841/1133	74.2 (71.6, 76.8)	0.1 (-3.5, 3.7)

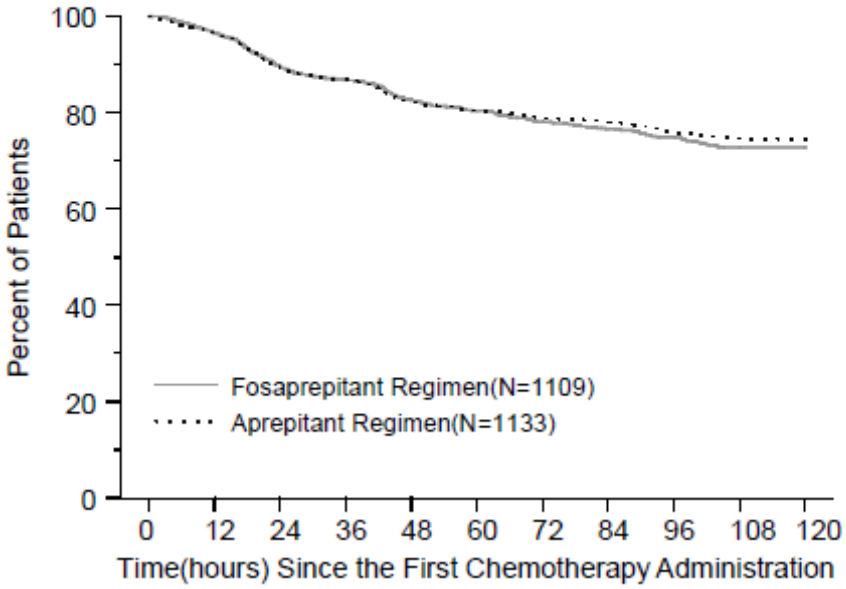
† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
Complete response = no vomiting and no use of rescue therapy.
Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.
Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.
Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.
n/m = Number of patients with Complete response/number of patients included in the analysis.

Table 6. Number (%) of Patients with Complete Response in the Overall and Delayed Phases by Treatment Group with the Difference Between Treatment Groups - Per Protocol Patient Population

Phase	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)	Difference† (A-B) %	(95% CI)†
Overall Phase	760/1061 (71.6)	790/1099 (71.9)	-0.3	(-4.0, 3.5)
Delayed Phase	786/1061 (74.1)	811/1098 (73.9)	0.2	(-3.5, 3.9)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
Complete response = no vomiting and no use of rescue therapy.
Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.
Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.
n/m = Number of patients with Complete response/number of patients included in the analysis.

Kaplan-Meier Curves for Time to First Vomiting Episode
From Start of Chemotherapy Administration in the Overall Phase
(Full Analysis Set Patient Population)



Exploratory endpoints

The FLIE is a self-administered, validated emesis- and nausea-specific questionnaire. Patients completed the questionnaire 5 days after receiving chemotherapy (Day 6). The questionnaire had 9 questions (items) on nausea (nausea domain) and 9 questions on vomiting (vomiting domain). No impact of CINV on daily life was defined as an average item score of >6 on the 7-point scale (i.e., >108 total score or >54 domain score).

The percent of patients with no impact of CINV on daily life by treatment group is summarized below.

Table 7. Percent of Patients With "No Impact of CINV on Daily Life†" by Treatment Group - Overall Phase - Full Analysis Set Patient Population

	FLIE Domain or Item Number	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)	Difference‡ (A-B)	95% CI‡ Difference
Total Score					
Nausea and Vomiting Specific	Total Score	748/1083 (69.1)	776/1108 (70.0)	-1.0	(-4.8, 2.9)
Domain and Item Scores					
Nausea-specific	Nausea Domain	710/1084 (65.5)	708/1108 (63.9)	1.6	(-2.4, 5.6)
Nausea-specific 'ability to enjoy daily meal'	Item 4	731/1084 (67.4)	738/1107 (66.7)	0.8	(-3.2, 4.7)
Nausea-specific 'daily functioning'	Item 7	773/1084 (71.3)	771/1108 (69.6)	1.7	(-2.1, 5.5)
Nausea-specific 'personal hardship'	Item 8	742/1084 (68.5)	747/1107 (67.5)	1.0	(-2.9, 4.9)
Vomiting-specific	Vomiting Domain	852/1084 (78.6)	904/1108 (81.6)	-3.0	(-6.3, 0.4)
Vomiting-specific 'ability to enjoy daily meal'	Item 13	889/1084 (82.0)	941/1107 (85.0)	-3.0	(-6.1, 0.1)
Vomiting-specific 'daily functioning'	Item 16	898/1081 (83.1)	961/1105 (87.0)	-3.9	(-6.9, -0.9)
Vomiting-specific 'hardship on other people'	Item 18	899/1081 (83.2)	951/1105 (86.1)	-2.9	(-5.9, 0.1)

† No Impact of CINV on Daily Life is defined as an average item score of >6 on the 7 point scale.

‡ The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

CINV = Chemotherapy-induced nausea and vomiting.

FLIE = Functional Living Index-Emesis.

n/m = Number of patients with No Impact of CINV on Daily Life/number of patients included in the analysis of the item.

Table 8. Number (%) of Patients with Complete Response by Day and Treatment Group - Per Protocol Patient Population

	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)
Day 1	942/1057 (89.1)	958/1090 (87.9)
Day 2	905/1058 (85.5)	914/1093 (83.6)
Day 3	892/1056 (84.5)	930/1101 (84.5)
Day 4	876/1050 (83.4)	911/1089 (83.7)
Day 5	935/1060 (88.2)	984/1093 (90.0)

Complete response = no vomiting and no use of rescue therapy.

n/m = Number of patients with Complete Response/number of patients included in the time-point.

2.5. Discussion & Conclusion on Clinical Efficacy

The selected experimental and control regimens of study P017L1 were considered justified, the inclusion/exclusion criteria were considered adequate and the outcome measures are standard, sufficiently sensitive and adequate for a non-inferiority study. And while the primary efficacy measure

could be criticized for not focusing on the delayed phase, altogether the overall design and the selected chemotherapy regimens and the (fos)aprepitant regimens were considered appropriate by CHMP.

With respect to gender and age, the patient population is considered representative for patients undergoing cisplatin-based chemotherapy (NSCLC). From a non-inferiority perspective more women and more patients below 55 years of age would have been preferable, but it is acknowledged that with respect to these covariates the population is similar to the patients enrolled in the pivotal trials in the aprepitant aplication.

Aprepitant was the first (2003) NK1 receptor antagonist licensed for the treatment of CINV (chemotherapy induced nausea and vomiting). Pivotal for licensure were two add-on studies to standard of care where an oral three-day regimen in both studies showed an add-on activity with respect to complete response of about 20%. In the pooled analysis the lower 95% CI for add-on activity was 14%.

The pivotal study for this application (P017L1) was conducted in a study population similar to the pivotal aprepitant studies, the chemotherapy regimens were similarly cisplatin-based and the study is considered to be of high quality with respect to planning and conduct and thus suitable as a single, pivotal non-inferiority study.

Of note chemotherapy regimens of moderate or high emetogenicity (per Hesketh Classification) were not allowed during the 6 days following cisplatin infusion. This, however, was the case also in the pivotal aprepitant studies

In the FAS, as well as the Per Protocol patient population, the pre-defined non-inferiority objective was met and the "possible" difference of about 4% is considered clinically insignificant. Also with respect to secondary outcome measures, including those focusing on control of nausea and emesis during the delayed phase of CINV, the objective of showing non-inferiority is considered fulfilled. The time to first vomiting event plots also support a non-inferiority conclusion.

No non-inferiority margin was predefined with respect to FLIE and "no impact of CINV on daily life", but the observed outcome may be compared with the pooled outcome in pivotal studies (P052 and P054). Also with respect to this outcome measure, it appears reasonable to conclude that overall non-inferiority has been shown, even though trends towards worse results in the vomiting specific domain have been noted.

2.5.1. Clinical safety

The overall safety of the multiple day aprepitant regimens were evaluated in approximately 6,500 individuals participating in clinical trials. In addition, fosaprepitant 115 mg IV infused over 15 minutes has been approved as an alternative for 125 mg oral aprepitant on Day 1 of the 3-day aprepitant regimen. Pivotal for the assessment of safety for this application (the 150 mg strength) is however the randomized comparative study P017LI.

Patient exposure

In Study P017L1, a total of 2,322 patients were randomized to receive either the fosaprepitant regimen (fosaprepitant, ondansetron, dexamethasone) (n=1,147) or the aprepitant regimen (aprepitant, ondansetron, dexamethasone) (n=1,175). Four patients in the fosaprepitant group and six patients in the aprepitant group did not take study medication and were excluded from the AE population.

As (fos)aprepitant were used as add-on to a high-dosed ondansetrone standard regimen in the context of cisplatin-based chemotherapy, it is hard to disentangle events causally related to (fos)aprepitant therapy.

Adverse events

Table 9. Adverse Event Summary P017L1

	Fosaprepitant Regimen (A) n	(%)	Aprepitant Regimen (B) n	(%)	Difference[§] (A-B)	95% CI[§] for the Difference
Patients in population	1,143		1,169			
with one or more adverse events	671	(58.7)	718	(61.4)	-2.7	(-6.7, 1.3)
with no adverse event	472	(41.3)	451	(38.6)		
with drug-related[†] adverse events	87	(7.6)	87	(7.4)	0.2	(-2.0, 2.3)
with serious adverse events	148	(12.9)	157	(13.4)	-0.5	(-3.3, 2.3)
with serious drug-related adverse events	4	(0.4)	7	(0.6)	-0.2	(-0.9, 0.4)
who died	23	(2.0)	26	(2.2)	-0.2	(-1.4, 1.0)
discontinued[‡] due to an adverse event	11	(1.0)	7	(0.6)	0.4	(-0.4, 1.2)
discontinued due to a drug-related adverse event	2	(0.2)	3	(0.3)	-0.1	(-0.6, 0.4)
discontinued due to a serious adverse event	8	(0.7)	4	(0.3)	0.4	(-0.3, 1.1)
discontinued due to a serious drug-related adverse event	1	(0.1)	2	(0.2)	-0.1	(-0.5, 0.3)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
[§]Calculated using the method of Miettinen and Nurminen.

Patients With Specific Adverse Events By System Organ Class (Incidence ≥ 1% in One or More Treatment Groups)

	Fosaprepitant Regimen (A) n	(%)	Aprepitant Regimen (B) N	(%)	Difference† (A-B)	95% CI for the Difference† (A-B)
Patients in population	1,143		1,169			
with one or more adverse events	671	(58.7)	718	(61.4)		
with no adverse events	472	(41.3)	451	(38.6)		
Blood and lymphatic system disorders	**96**	**(8.4)**	**98**	**(8.4)**	**0.0**	**(-2.3, 2.3)**
Anaemia	20	(1.7)	10	(0.9)	0.9	(0.0, 1.9)
Febrile neutropenia	20	(1.7)	30	(2.6)	-0.8	(-2.1, 0.4)
Leukopenia	18	(1.6)	18	(1.5)	0.0	(-1.0, 1.1)
Neutropenia	45	(3.9)	38	(3.3)	0.7	(-0.9, 2.3)
Thrombocytopenia	19	(1.7)	16	(1.4)	0.3	(-0.7, 1.4)
Cardiac disorders	**14**	**(1.2)**	**11**	**(0.9)**	**0.3**	**(-0.6, 1.2)**
Ear and labyrinth disorders	**32**	**(2.8)**	**23**	**(2.0)**	**0.8**	**(-0.4, 2.1)**
Tinnitus	19	(1.7)	10	(0.9)	0.8	(-0.1, 1.8)
Gastrointestinal disorders	**381**	**(33.3)**	**400**	**(34.2)**	**-0.9**	**(-4.7, 3.0)**
Abdominal pain	35	(3.1)	38	(3.3)	-0.2	(-1.7, 1.3)
Abdominal pain upper	46	(4.0)	30	(2.6)	1.5	(0.0, 3.0)
Constipation	121	(10.6)	112	(9.6)	1.0	(-1.5, 3.5)
Diarrhoea	89	(7.8)	102	(8.7)	-0.9	(-3.2, 1.3)
Dyspepsia	50	(4.4)	38	(3.3)	1.1	(-0.4, 2.7)
Gastritis	12	(1.0)	10	(0.9)	0.2	(-0.6, 1.1)
Nausea	68	(5.9)	81	(6.9)	-1.0	(-3.0, 1.0)
Stomatitis	20	(1.7)	19	(1.6)	0.1	(-1.0, 1.2)
Vomiting	75	(6.6)	65	(5.6)	1.0	(-1.0, 3.0)
General disorders and administration site conditions	**243**	**(21.3)**	**283**	**(24.2)**	**-2.9**	**(-6.4, 0.5)**
Asthenia	98	(8.6)	136	(11.6)	-3.1	(-5.5, -0.6)
Chest pain	16	(1.4)	19	(1.6)	-0.2	(-1.3, 0.8)
Fatigue	53	(4.6)	57	(4.9)	-0.2	(-2.0, 1.5)
Infusion site pain	16	(1.4)	1	(0.1)	1.3	(0.7, 2.2)
Mucosal inflammation	25	(2.2)	34	(2.9)	-0.7	(-2.1, 0.6)
Pain	12	(1.0)	12	(1.0)	0.0	(-0.9, 0.9)
Pyrexia	23	(2.0)	25	(2.1)	-0.1	(-1.3, 1.1)
Infections and infestations	**71**	**(6.2)**	**76**	**(6.5)**	**-0.3**	**(-2.3, 1.7)**
Urinary tract infection	11	(1.0)	3	(0.3)	0.7	(0.1, 1.5)
Injury, poisoning and procedural complications	**12**	**(1.0)**	**22**	**(1.9)**	**-0.8**	**(-1.9, 0.2)**
Accidental overdose	11	(1.0)	13	(1.1)	-0.2	(-1.0, 0.7)
Investigations	**72**	**(6.3)**	**84**	**(7.2)**	**-0.9**	**(-3.0, 1.2)**
Alanine aminotransferase increased	16	(1.4)	17	(1.5)	-0.1	(-1.1, 1.0)
Blood creatinine increased	16	(1.4)	13	(1.1)	0.3	(-0.7, 1.3)

Patients With Specific Adverse Events By System Organ Class
(Incidence ≥ 1% in One or More Treatment Groups) (Cont.)

	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference†	95% CI for the Difference†
	n	(%)	N	(%)	(A-B)	(A-B)
Metabolism and nutrition disorders	**142**	**(12.4)**	**187**	**(16.0)**	**-3.6**	**(-6.4, -0.7)**
Anorexia	76	(6.6)	106	(9.1)	-2.4	(-4.6, -0.2)
Dehydration	32	(2.8)	41	(3.5)	-0.7	(-2.2, 0.7)
Hypokalaemia	13	(1.1)	11	(0.9)	0.2	(-0.7, 1.1)
Hyponatraemia	15	(1.3)	15	(1.3)	0.0	(-0.9, 1.0)
Musculoskeletal and connective tissue disorders	**50**	**(4.4)**	**65**	**(5.6)**	**-1.2**	**(-3.0, 0.6)**
Myalgia	16	(1.4)	17	(1.5)	-0.1	(-1.1, 1.0)
Pain in extremity	18	(1.6)	16	(1.4)	0.2	(-0.8, 1.3)
Nervous system disorders	**121**	**(10.6)**	**118**	**(10.1)**	**0.5**	**(-2.0, 3.0)**
Dizziness	38	(3.3)	35	(3.0)	0.3	(-1.1, 1.8)
Dysgeusia	14	(1.2)	14	(1.2)	0.0	(-0.9, 1.0)
Headache	46	(4.0)	48	(4.1)	-0.1	(-1.7, 1.6)
Psychiatric disorders	**30**	**(2.6)**	**40**	**(3.4)**	**-0.8**	**(-2.2, 0.6)**
Insomnia	14	(1.2)	19	(1.6)	-0.4	(-1.4, 0.6)
Renal and urinary disorders	**28**	**(2.4)**	**32**	**(2.7)**	**-0.3**	**(-1.6, 1.0)**
Respiratory, thoracic and mediastinal disorders	**138**	**(12.1)**	**140**	**(12.0)**	**0.1**	**(-2.6, 2.8)**
Cough	26	(2.3)	22	(1.9)	0.4	(-0.8, 1.6)
Dyspnoea	18	(1.6)	20	(1.7)	-0.1	(-1.2, 1.0)
Hiccups	64	(5.6)	74	(6.3)	-0.7	(-2.7, 1.2)
Skin and subcutaneous tissue disorders	**51**	**(4.5)**	**60**	**(5.1)**	**-0.7**	**(-2.4, 1.1)**
Alopecia	12	(1.0)	16	(1.4)	-0.3	(-1.3, 0.6)
Erythema	13	(1.1)	5	(0.4)	0.7	(0.0, 1.6)
Vascular disorders	**65**	**(5.7)**	**45**	**(3.8)**	**1.8**	**(0.1, 3.6)**
Hypertension	17	(1.5)	7	(0.6)	0.9	(0.1, 1.8)
Hypotension	12	(1.0)	14	(1.2)	-0.2	(-1.1, 0.8)

† Calculated by the method of Miettinen and Nurminen.
Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Infusion-site reactions (Primary safety endpoint)

Potential concerns for safety and tolerability that may be unique to fosaprepitant intravenous formulation as compared to oral aprepitant include reactions at the injection site. Therefore, reactions at the injection site were prespecified events of clinical interest for P017L1 to test the hypothesis that the single-dose fosaprepitant dimeglumine regimen is well tolerated in the first cycle of cisplatin-based HEC.

Table 10. Patients With Infusion-Site Adverse Events By System Organ Class (Incidence > 0% in One or More Treatment Groups) Treated Patients

	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference[§] (A-B)	95% CI[§] for the Difference	p-value†
	n	(%)	n	(%)			
Patients in population	1,143		1,169				
with one or more injection site adverse events	11	(1.0)	1	(0.1)			
with no injection site adverse events	1,132	(99.0)	1,168	(99.9)			
General disorders and administration site conditions	**2**	**(0.2)**	**0**	**(0.0)**			
Infusion site pain	2	(0.2)	0	(0.0)	0.2	(-0.15, 0.64)	0.076
Vascular disorders	**9**	**(0.8)**	**1**	**(0.1)**			
Thrombophlebitis	9	(0.8)	1	(0.1)	0.7	(0.21, 1.41)	0.005

†Calculated using method of Miettinen and Nurminen.
Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

All cases were classified as non-serious. Out of the 9 cases of thrombophlebitis, five were characterized as moderate in severity. According to investigator assessment 5 out of the 9 cases of thrombophlebitis were related to chemotherapy and eight out of 9 cases recovered or resolved. The remaining patient was characterized as resolving, but the adverse event did not completely resolve by the time of the study completion. This patient's adverse event was characterized as mild and the adverse event was characterized as being related to both the administration of cisplatin and study medication by the investigator.

Hypersensitivity reactions

Post-marketing safety reports received by the MAH indicate a possible relationship between hypersensitivity reactions in patients administered fosaprepitant 115 mg.

Since market introduction of fosaprepitant (cumulative data from market introduction on 26-Mar-2003 through 30-Jun-2009), 26 reports of hypersensitivity reactions were identified in which onset occurred on Day 1, thereof 12 reports in which the event or events occurred within a few minutes of initiation of administration suggesting an immediate hypersensitivity reaction.

In 9 of these 12 reports there was an immediate hypersensitivity event or events after exposure to IV fosaprepitant only (patients did not receive oral aprepitant before or after therapy with fosaprepitant), 8 of these events resulted in discontinuation of therapy and in 1 of these 9 reports the patient successfully tolerated restarting the infusion. In another 1 of these 12 reports the patient had previously tolerated oral aprepitant and then had a hypersensitivity event after exposure to IV fosaprepitant. In the last 2 reports the patients subsequently tolerated oral aprepitant after having a hypersensitivity related event when exposed to IV fosaprepitant. In these cases, the most commonly reported adverse events were flushing, erythema and dyspnoea. The patients generally responded to discontinuation of the fosaprepitant infusion and initiation of appropriate therapy(ies).

In order to evaluate the possibility of increased hypersensitivity to fosaprepitant and/or an excipient in the formulation, a post-hoc review of potential hypersensitivity adverse events in P017L1 was conducted.

Table 11. Number of Potential Hypersensitivity Adverse Events by Treatment Group (P017L1)

	Fosaprepitant	Aprepitant
Number of events of hypersensitivity	46	39
Serious AE	0	2 (5%)
AE Related to study medication	8 (9%)	7 (18%)
AE mild	38 (83%)	30 (77%)
AE moderate	8 (17%)	8 (21%)
AE severe	0	1 (2.6%)
Number of hypersensitivity adverse events presented on Day 1 of study medication	14 (30%)	7 (18%)
Number of hypersensitivity adverse events presented on Day 2 of study medication	8 (17%)	3 (8%)
Number of hypersensitivity adverse events presented on Day 3-17 of study medication	24 (52%)	29 (74%)

One patient treated with the fosaprepitant regimen had a non-serious adverse event of chest discomfort, facial flushing and tightness in the throat that resulted is discontinuation of study medication. This adverse event occurred on the same day that study medication was administered, and was thought to be related to study medication.

The potential hypersensitivity adverse events for patients treated with fosaprepitant were mostly non serious, mostly mild, and were medically managed without significant patient sequelae. The results of the analysis of potential hypersensitivity adverse events are consistent with the available post marketing data for patients treated with fosaprepitant 115 mg.

Serious adverse event/deaths/other significant events

The overall incidence of serious adverse events was similar in both treatment groups (fosaprepitant 12.9%; aprepitant 13.4%). In general, the serious adverse profile was typical of a patient population with cancer receiving highly emetogenic chemotherapy.

23 patients treated with fosaprepitant and 26 patients treated with aprepitant died during the observation period of the study. None of these adverse events resulting in death were considered drug related by the investigator, and all were consistent with the natural history of patients with cancer receiving chemotherapy.

Laboratory findings

ALT and AST increase are events listed as common for aprepitant. However, more patients in the fosaprepitant group experienced ALT (and AST) increase.

Table 12. Number (%) of Patients with Elevated ALT>5X ULN Post Treatment P017L1

Laboratory Test Results	Fosaprepitant	Aprepitant
ALT>5 X ULN	20/1112 (1.8%)	6/1137 (1.3%)
ALT>5 X ULN with baseline ALT>ULN	12/20 (60%)	3/6 (50%)
ALT>5 X ULN with an underlying hepatobiliary disease	6/20 (30%)	2/6 (33%)
ALT>5 X ULN with an adverse event related to increase liver function tests	4/20 (20%)	1/6 (17%)
ALT>5 X ULN Day 6-8 post treatment	15/20 (75%)	6/6 (100%)
ALT>5 X ULN Day 9-13 post treatment	3/20 (15%)	0

ALT>5 X ULN Day 14-29 post treatment	2/20 (10%)	0
ALT>5 X ULN with ALT ≤ 3 X ULN on Day 14-29	15/20 (75%)	6/6 (100%)
ALT>5 X ULN with Total serum bilirubin >2 X ULN	0	1
ALT>5 X ULN with AST >5 X ULN	4/20 (20%)	1/6 (17%)

2.6. Discussion & Conclusion on Clinical Safety

Fosaprepitant 115 mg is licensed as an alternative to aprepitant 125 mg day 1. This application refers to an increase in dose to 150 mg IV in order to cover the full period of CINV. No peak associated adverse reactions have previously been seen, but dose related local reactions. Therefore the duration of the infusion was increased for the 150 mg dose (20-30 min) compared with the 115 mg dose (15 min).

In study P017L1 no likely informative differences were detected in the AE summary between the treatment arms.

Among adverse reactions listed as common for aprepitant, however, asthenia was reported less often in the fosaprepitant arm. Numerically less often also hiccup, headache and diarrhoea, while constipation was more frequently reported in the fosaprepitant arm. Infusion site pain was reported in 1.4% vs. 0.1, fosaprepitant vs. aprepitant. Overall, differences are small.

Compared with placebo a modest increase of injection site reactions was documented.

Available data, including post marketing reports, indicate that infusion of fosaprepitant is associated with hypersensitivity reactions, mainly of mild character and at an incidence considered clinically acceptable.

There is a signal compatible with an increased incidence of ALT/AST elevations compared with aprepitant. The most likely reason, however, is baseline imbalances with respect to underlying hepatic conditions.

Compared with the licensed oral aprepitant three-day regimen, fosaprepitant 150 mg administered once on day 1, there are only minor safety differences. Immediate hypersensitivity reactions have been reported, injection site reactions too, but incidence and grade are considered to have only a minor impact on the relative risk profile. Some events were reported less frequently in association with fosaprepitant such as asthenia. Overall fosaprepitant is considered to have a favourable safety profile.

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system (DDPS version 6.0, dated 22nd June 2009) as described by the applicant fulfils the legislative requirements.

2.7.2. Risk management plan

The MAA submitted a risk management plan (version no. 3.1 dated 23 June 2010).

Summary of the Risk Management Plan – Fosaprepitant

Safety Concern	Proposed Pharmacovigilance	Proposed Risk Minimisation Activities (routine and additional)

	Activities (routine and additional)	
Important Identified Risks		
Local tolerability	• Routine Pharmacovigilance • Monitor reports of local tolerability from ongoing clinical trials	• EUSPC Section 4.4 (Special warning and precautions for use): Administration and infusion site reactions: IVEMEND should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see section 4.2). IVEMEND should not be administered intramuscularly or subcutaneously (see section 5.3). Mild injection site thrombosis has been observed at higher doses (see section 4.9). If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein. • Listed as ADE under SPC section 4.8 • EUSPC Section 5.3 (Pre-clinical safety data): In rabbits, IVEMEND caused initial transient local acute inflammation following paravenous, subcutaneous and intramuscular administration. At the end of the follow-up period (post-dose day 8), local subacute inflammation was noted following paravenous and intramuscular administration and additional focal muscle degeneration/necrosis following intramuscular administration, with evidence of ongoing resolutionat the injection sites.
Hypersensitivity	• Routine pharmacovigilance • Monitor reports of hypersensitivity from ongoing clinical trials	• EUSPC Section 4.3 (Contraindications): Hypersensitivity to fosaprepitant, aprepitant, or to polysorbate 80 or any of the excipients. • EUSPC Section 4.4 (Special warning and precautions for use): Hypersensitivity reactions: Isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnea have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. It is not recommended to reinitiate the infusion in patients who experience hypersensitivity reactions. • Listed as ADE under SPC section 4.8
Drug interaction: reduction of efficacy of hormonal contraceptives	The Sponsor will continue to monitor post marketing reports of drug interaction and describe them in the	• EUSPC Section 4.4 (Special warning and precautions for use): Coadministration with hormonal contraceptives: The efficacy of hormonal contraceptives may be reduced during and for 28 days after

	PSURs	administration of fosaprepitant. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 2 months following the use of fosaprepitant. • EUSPC Section 4.5 (Interaction with other medicinal products and other forms of interaction); Hormonal contraceptives: The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of fosaprepitant. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 2 months following the use of fosaprepitant .
Important Potential Risks		
Potential for medication error	• Routine pharmacovigilance	• EUSPC Section 4.2 (Posology and method of administration): *Since IVEMEND is also available as a 115 mg vial, it is important to note that the preparation (volume for dilution), infusion rate and doses of concomitant therapy for IVEMEND 150 mg are different from those for IVEMEND 115 mg. See also section 6.6 for preparation. *Oral aprepitant on Days 2 and 3 is only administered in combination with IVEMEND 115 mg on Day 1. No aprepitant is administered orally in combination with IVEMEND 150 mg. *The recommended dose of dexamethasone with IVEMEND 150 mg differs from the recommended dose of dexamethasone with IVEMEND 115 mg on Days 3 and 4. Special precautions for disposal and other handling under SPC section 6.6. Note that the preparation (volume for dilution), infusion rate and doses of concomitant therapy for IVEMEND 150 mg are different from those for IVEMEND 115 mg. Oral aprepitant on Days 2 and 3 is only administered in combination with IVEMEND 115 mg on Day 1. No aprepitant is administered orally in combination with IVEMEND 150 mg. The recommended dose of dexamethasone with IVEMEND 150 mg differs from the recommended dose of dexamethasone with IVEMEND 115 mg on Days 3 and 4. • EUSPC Section 6.6 (Special precautions for disposal and other handling):

		IVEMEND must be reconstituted and then diluted prior to administration. **Note that the preparation (volume for dilution), infusion rate and doses of concomitant therapy for IVEMEND 150 mg are different from those for IVEMEND 115 mg. See also section 4.2 for posology and method of administration.** Preparation of IVEMEND 150 mg for intravenous administration: 1. Inject 5 ml sodium chloride 9 mg/ml (0.9 %) solution for injection into the vial. Assure that sodium chloride 9 mg/ml (0.9 %) solution for injection is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting sodium chloride 9 mg/ml (0.9 %) solution for injection into the vial. 2. Prepare an infusion bag filled with **145 ml** of sodium chloride 9 mg/ml (0.9 %) solution for injection (for example, by removing 105 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection from a 250 ml sodium chloride 9 mg/ml (0.9 %) solution for injection infusion bag). 3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection to **yield a total volume of 150 ml**. Gently invert the bag 2-3 times.
Important Missing Information		
Use in pregnancy	Routine pharmacovigilance monitoring in pregnant and lactating women	• Statement under SPC section 4.6 (Pregnancy and Lactation), Pregnancy: For fosaprepitant and aprepitant no clinical data on exposed pregnancies are available. The potential for reproductive toxicities of fosaprepitant and aprepitant have not been fully characterised, since exposure levels above the therapeutic exposure in humans could not be attained in animal studies. These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development

		(see section 5.3). The potential effects on reproduction of alterations in neurokinin regulation are unknown. IVEMEND should not be used during pregnancy unless clearly necessary. • Breast-feeding: Aprepitant is excreted in the milk of lactating rats after intravenous administration of fosaprepitant as well as after oral administration of aprepitant**.** It is not known whether aprepitant is excreted in human milk. Therefore, breast-feeding is not recommended during treatment with IVEMEND and oral aprepitant. • Section 5.3 (pre-clinical safety data)Pre-clinical data obtained with intravenous administration of fosaprepitant and oral administration of aprepitant reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity (including *in vitro* tests), and toxicity to reproduction.
Use in patients < 18 years of age	• Routine pharmacovigilance monitoring in patients less than 18 years of age • Monitoring of adverse effects in ongoing pharmacokinetic studies in patients <18 years of age	• SPC section 4.2 (Posology and Method of Administration) <u>Paediatric population</u> The safety and efficacy of IVEMEND in children and adolescents below the age of 18 years of age has not yet been established. No data are available. • Section 5.1 (Pharmacodynamic properties), and Package Leaflet <u>Paediatric population</u> Studies evaluating the use of fosaprepitant in paediatric patients are on-going (see section 4.2 for information on paediatric use).
Use in patients with moderate or severe hepatic impairment	• Routine pharmacovigilance monitoring in patients with moderate or severe hepatic impairment	• EUSPC Section 4.2 (Posology and method of administration): *Hepatic impairment:* No dose adjustment is necessary for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. IVEMEND should be used with caution in these patients. • EUSPC Section 4.4 (Special warning and precautions for use): *Patients with moderate to severe hepatic impairment:* There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. IVEMEND should be used with caution in these patients.

		• EUSPC Section 5.2 (Pharmacokinetic properties). *Hepatic impairment:* Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant. Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a clinically relevant extent. No dose adjustment is necessary for patients with mild hepatic impairment. Conclusions regarding the influence of moderate hepatic impairment (Child-Pugh class B) on aprepitant pharmacokinetics cannot be drawn from available data. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh class C).

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.

2.7.2.1. User consultation

No user consultation for the IVEMEND package leaflet has been performed. The applicant had argued that since no significant change have been made to the PL, it was considered appropriate to use the evidence from a readability testing performed on a reference PL (EMEND PL) for the 150 mg IVEMEND PL part of the line extension application. This approach was not accepted by CHMP. The Applicant is asked to submit a full user testing report (as per the readability guideline) as a FUM. This is based on the fact that the package leaflet for IVEMEND has not been user tested before, neither for the 115 mg nor the 150 mg version. Furthermore, the risk of medication errors between the two strengths is considered high.

2.7.3. Benefit-risk balance

Benefits

Fosaprepitant, at a dose of 150 mg administered as a single infusion over 20 to 30 minutes, provides a similarly effective alternative to the approved 3-day regimen of aprepitant.

Unfavourable effects

Compared with placebo a modest increase of injection site reactions was documented. Available data, including post marketing reports, indicate that infusion of fosaprepitant (also the licensed 115 mg formulation) is associated with hypersensitivity reactions, mainly of mild character and at an incidence considered clinically acceptable.

Uncertainty in the knowledge about the unfavourable effects

There is a signal related to an apparent increase in hepatic enzyme adverse events in patients administered fosaprepitant 150 mg compared with aprepitant. Confounding factors are considered the most likely reason for this.

Benefit-risk balance

Ivemend administered in a single dose of 150 mg as add-on a 5HT3 antagonist/glucorticosteroid regimen for the treatment of CINV has a favourable benefit – risk profile which is similar to the currently licensed 3-day regimen of aprepitant.

Discussion on the benefit-risk balance

The overall benefit–risk profile of Ivemend 150 mg is positive. All comments to the product information have been addressed satisfactorily;The applicant has provided a Letter of Undertaking committing to perform the post-authorisation follow up measures as detailed in section 2.6 in the agreed timeframes.

Risk management plan

A risk management plan was submitted (version 3.1 dated 23 June 2010). 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.

2.7.4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Ivemend 150 mg powder for solution for infusion in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults, the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults given as part of a combination therapy was favourable and therefore recommended the granting of the marketing authorisation.