ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IVEMEND 150 mg powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant, which corresponds to 130.5 mg of aprepitant. After reconstitution and dilution 1 ml of solution contains 1 mg fosaprepitant (1 mg/ml) (see section 6.6).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.
White to off-white amorphous powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and paediatric patients aged 6 months and older.

IVEMEND 150 mg is given as part of a combination therapy (see section 4.2).

4.2 Posology and method of administration

Posology
Adults
The recommended dose is 150 mg administered as an infusion **over 20-30 minutes** on Day 1, initiated approximately 30 minutes prior to chemotherapy (see section 6.6). IVEMEND should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in the tables below.

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

Table 1: Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy regimen in adults

	Day 1	**Day 2**	**Day 3**	**Day 4**
IVEMEND	150 mg intravenously	none	none	none
Dexamethasone	12 mg orally	8 mg orally	**8 mg orally twice daily**	**8 mg orally twice daily**
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information	none	none	none

Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 to 4. Dexamethasone should also be administered in the evenings on Days 3 and 4. The dose of dexamethasone accounts for active substance interactions.

Table 2: Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy regimen in adults

	Day 1
IVEMEND	150 mg intravenously
Dexamethasone	12 mg orally
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information

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

Paediatric population

Paediatric patients aged 6 months and older, and not less than 6 kg

The recommended dose regimen of IVEMEND, to be administered with a 5-HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemotherapy regimens of Highly Emetogenic Chemotherapy (HEC) or Moderately Emetogenic Chemotherapy (MEC), is shown in Table 3. Single day chemotherapy regimens include those regimens in which HEC or MEC is administered for a single day only. Multi-day chemotherapy regimens include chemotherapy regimens in which HEC or MEC is administered for 2 or more days.

An alternative dose regimen that may be used with single day chemotherapy regimens is shown in Table 4.

Dosing for Single or Multi-Day Chemotherapy Regimens
For paediatric patients receiving single or multi-day regimens of HEC or MEC, administer IVEMEND as an intravenous infusion through a central venous catheter on Days 1, 2, and 3. EMEND capsules or EMEND for oral suspension may be used on Days 2 and 3 instead of IVEMEND, as shown in Table 3. See the Summary of Product Characteristics (SmPC) for EMEND capsules or EMEND for oral suspension for appropriate dosing instructions.

Table 3: Recommended dosing for the prevention of nausea and vomiting associated with single or multi-day regimens of HEC or MEC in paediatric patients

	Population	**Day 1**	**Day 2**	**Day 3**
IVEMEND*	Paediatric patients 12 years and older	115 mg intravenously	80 mg intravenously OR 80 mg orally (EMEND capsules)	80 mg intravenously OR 80 mg orally (EMEND capsules)
	Paediatric patients 6 months to less than 12 years and not less than 6 kg	3 mg/kg intravenously Maximum dose 115 mg	2 mg/kg intravenously OR 2 mg/kg orally (EMEND oral suspension) Maximum dose 80 mg	2 mg/kg intravenously OR 2 mg/kg orally (EMEND oral suspension) Maximum dose 80 mg
Dexamethasone**	All paediatric patients	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on days 1 through 4		
5-HT_3 antagonist	All paediatric patients	See selected 5-HT_3 antagonist prescribing information for the recommended dosage		

* For paediatric patients 12 years and older, administer IVEMEND intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy. For paediatric patients less than 12 years, administer IVEMEND intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.
** **Dexamethasone** should be administered 30 minutes prior to chemotherapy treatment on Day 1.

Alternative Dosing for Single Day Chemotherapy Regimens
For paediatric patients receiving single day HEC or MEC, IVEMEND may be administered as an intravenous infusion through a central venous catheter on Day 1.

Table 4: Alternative dosing for the prevention of nausea and vomiting associated with single day regimens of HEC or MEC in paediatric patients

	Population	Day 1
IVEMEND*	Paediatric patients 12 years and older	150 mg intravenously
	Paediatric patients 2 to less than 12 years	4 mg/kg intravenously Maximum dose 150 mg
	Paediatric patients 6 months to less than 2 years and not less than 6 kg	5 mg/kg intravenously Maximum dose 150 mg
Dexamethasone**	All paediatric patients	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on days 1 and 2.
5-HT_3 antagonist	All paediatric patients	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

* For paediatric patients 12 years and older, administer IVEMEND intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy. For paediatric patients less than 12 years, administer IVEMEND intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy.
** **Dexamethasone** should be administered 30 minutes prior to chemotherapy treatment on Day 1.

The safety and efficacy of IVEMEND in infants below 6 months of age have not been established. No data are available.

<u>*General*</u>
Efficacy data in combination with other corticosteroids and 5-HT_3 antagonists are limited. For additional information on the co-administration with corticosteroids, see section 4.5.

Refer to the Summary of Product Characteristics of co-administered 5-HT_3 antagonist medicinal products.

<u>*Special populations*</u>
Elderly (≥65 years)
No dose adjustment is necessary for the elderly (see section 5.2).

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

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

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

<u>Method of administration</u>
IVEMEND 150 mg should be administered intravenously and should not be given by the intramuscular or subcutaneous route. Intravenous administration in adults occurs preferably through a

running intravenous infusion over 20-30 minutes. Intravenous administration in paediatric patients aged 6 months and older is recommended through a central venous catheter and should be administered over 30 minutes in patients aged 12 years and older or over 60 minutes in patients less than 12 years of age (see section 6.6). Do not administer IVEMEND as a bolus injection or undiluted solution.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to polysorbate 80 or any of the other excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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

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

Co-administration with warfarin (a CYP2C9 substrate)
In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely for 14 days following the use of fosaprepitant (see section 4.5).

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

Hypersensitivity reactions
Immediate hypersensitivity reactions including flushing, erythema, dyspnoea, and anaphylaxis/anaphylactic shock have occurred during or soon after 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.

Administration and infusion site reactions
Infusion site reactions (ISRs) have been reported with the use of IVEMEND (see section 4.8). The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (e.g., anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy. Mild injection site thrombosis has been observed at higher doses without concomitant vesicant chemotherapy.

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). If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

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

4.5 Interaction with other medicinal products and other forms of interaction

When administered intravenously fosaprepitant is rapidly converted to aprepitant.

Fosaprepitant 150 mg, given as a single dose, is a weak inhibitor of CYP3A4. Fosaprepitant does not seem to interact with the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin. It is anticipated that fosaprepitant would cause less or no greater induction of CYP2C9, CYP3A4 and glucuronidation than that caused by the administration of oral aprepitant. Data are lacking regarding effects on CYP2C8 and CYP2C19.

Interactions with other medicinal products following administration of intravenous fosaprepitant are likely to occur with active substances that interact with oral aprepitant. The potential for interactions with multi-day fosaprepitant regimens are anticipated to be no greater than those for oral aprepitant regimens. Therefore, the recommendations for use of IVEMEND with other medicinal products in paediatric patients are based upon adult data from fosaprepitant and aprepitant studies. When using combined IVEMEND and EMEND regimens, please refer to the Summary of Product Characteristics (SmPC) section 4.5 for EMEND capsules or EMEND for oral suspension.

The following information was derived from studies conducted with oral aprepitant and studies conducted with intravenous single dose fosaprepitant co-administered with dexamethasone, midazolam, or diltiazem.

Effect of fosaprepitant on the pharmacokinetics of other active substances
CYP3A4 inhibition
As a weak inhibitor of CYP3A4, the fosaprepitant 150 mg single dose can cause a transient increase in plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of CYP3A4 substrates may increase up to 2-fold on Days 1 and 2 after co-administration with a single 150 mg fosaprepitant dose. Fosaprepitant must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by fosaprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions (see section 4.3). Caution is advised during concomitant administration of fosaprepitant and active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as ciclosporin, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see section 4.4).

Corticosteroids
Dexamethasone: The oral dexamethasone dose should be reduced by approximately 50 % when co-administered with fosaprepitant (see section 4.2). Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, a CYP3A4 substrate, by 100 % on Day 1, 86 % on Day 2 and 18 % on Day 3 when dexamethasone was co-administered as a single 8 mg oral dose on Days 1, 2, and 3.

Chemotherapeutic medicinal products
Interaction studies with fosaprepitant 150 mg and chemotherapeutic medicinal products have not been conducted; however, based on studies with oral aprepitant and docetaxel and vinorelbine, IVEMEND 150 mg is not expected to have a clinically relevant interaction with intravenously administered docetaxel and vinorelbine. An interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g., etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolised primarily or partly by CYP3A4 (see section 4.4). Postmarketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration.

Immunosuppressants
Following a single 150 mg fosaprepitant dose, a transient moderate increase for two days possibly followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g., ciclosporin, tacrolimus, everolimus and sirolimus) is expected. Given the short duration of increased exposure, dose reduction of the immunosuppressant based on Therapeutic Dose Monitoring is not recommended on the day of and the day after administration of IVEMEND.

Midazolam
Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by 77 % on Day 1 and had no effect on Day 4 when midazolam was co-administered as a single oral dose of 2 mg on Days 1 and 4. Fosaprepitant 150 mg is a weak CYP3A4 inhibitor as a single dose on Day 1 with no evidence of inhibition or induction of CYP3A4 observed on Day 4.

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

Diltiazem
Interaction studies with fosaprepitant 150 mg and diltiazem have not been conducted; however, the following study with 100 mg of fosaprepitant should be considered when using IVEMEND 150 mg with diltiazem. In patients with mild to moderate hypertension, infusion of 100 mg of fosaprepitant over 15 minutes with diltiazem 120 mg 3 times daily, resulted in a 1.4-fold increase in diltiazem AUC and a small but clinically meaningful decrease in blood pressure, but did not result in a clinically meaningful change in heart rate, or PR interval.

Induction
The fosaprepitant 150 mg single dose did not induce CYP3A4 on Days 1 and 4 in the midazolam interaction study. It is anticipated that IVEMEND would cause less or no greater induction of CYP2C9, CYP3A4, and glucuronidation than that caused by the administration of the 3-day oral aprepitant regimen, for which a transient induction with its maximum effect 6-8 days after first aprepitant dose has been observed. The 3-day oral aprepitant regimen resulted in an about 30-35 % reduction in AUC of CYP2C9 substrates and up to a 64 % decrease in ethinyl estradiol trough concentrations. Data are lacking regarding effects on CYP2C8 and CYP2C19. Caution is advised when warfarin, acenocoumarol, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered with IVEMEND.

Warfarin
In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with and for 14 days following the use of IVEMEND for the prevention of chemotherapy induced nausea and vomiting (see section 4.4).

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

5-HT_3 antagonists
Interaction studies with fosaprepitant 150 mg and 5-HT_3 antagonists have not been conducted; however, in clinical interaction studies, the oral aprepitant regimen did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron). Therefore, there is no evidence of interaction with the use of IVEMEND 150 mg and 5-HT_3 antagonists.

Effect of other medicinal products on the pharmacokinetics of aprepitant resulting from administration of fosaprepitant 150 mg
Concomitant administration of fosaprepitant with active substances that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, and protease inhibitors) should be approached cautiously, as the combination is expected to result in several-fold increased plasma concentrations of aprepitant (see section 4.4). Ketoconazole increased the terminal half-life of oral aprepitant about 3-fold.

Concomitant administration of fosaprepitant with active substances that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination could result in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy. Concomitant administration of fosaprepitant with herbal preparations containing St. John's Wort (*Hypericum perforatum*) is not recommended. Rifampicin decreased the mean terminal half-life of oral aprepitant by 68 %.

Diltiazem
Interaction studies with fosaprepitant 150 mg and diltiazem have not been conducted; however, the following study with 100 mg of fosaprepitant should be considered when using IVEMEND 150 mg with diltiazem. Infusion of 100 mg fosaprepitant over 15 minutes with diltiazem 120 mg 3 times daily, resulted in a 1.5-fold increase of aprepitant AUC. This effect was not considered clinically important.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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

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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
In clinical studies, various formulations of fosaprepitant have been administered to a total of 2,687 adults including 371 healthy subjects and 2,084 patients, and 299 children and adolescents with chemotherapy induced nausea and vomiting (CINV). Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant are expected to occur with fosaprepitant. The safety profile of aprepitant was evaluated in approximately 6,500 adults and 184 children and adolescents.

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

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

Tabulated list of adverse reactions - aprepitant
The following adverse reactions were observed in a pooled analysis of the HEC and MEC studies at a greater incidence with oral aprepitant than with standard therapy in adults or paediatric patients or in post-marketing use.

The frequency categories given in the table are based on the studies in adults; the observed frequencies in the paediatric studies were similar or lower, unless shown in the table. Some less common ADRs in the adult population were not observed in the paediatric studies.

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

Table 5: Tabulated list of adverse reactions – aprepitant

System organ class	Adverse reaction	Frequency
Infection and infestations	candidiasis, staphylococcal infection	rare
Blood and lymphatic system disorders	febrile neutropenia, anaemia	uncommon
Immune system disorders	hypersensitivity reactions including anaphylactic reactions	not known
Metabolism and nutrition disorders	decreased appetite	common
	polydipsia	rare
Psychiatric disorders	anxiety	uncommon
	disorientation, euphoric mood	rare
Nervous system disorders	headache	common
	dizziness, somnolence	uncommon
	cognitive disorder, lethargy, dysgeusia	rare
Eye disorders	conjunctivitis	rare
Ear and labyrinth disorders	tinnitus	rare

System organ class	Adverse reaction	Frequency
Cardiac disorders	palpitations	uncommon
	bradycardia, cardiovascular disorder	rare
Vascular disorders	hot flush/flushing	uncommon
Respiratory, thoracic and mediastinal disorders	hiccups	common
	oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation	rare
Gastrointestinal disorders	constipation, dyspepsia	common
	eructation, nausea*, vomiting*, gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence	uncommon
	duodenal ulcer perforation, stomatitis, abdominal distension, faeces hard, neutropenic colitis	rare
Skin and subcutaneous tissue disorders	rash, acne	uncommon
	photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/toxic epidermal necrolysis	rare
	pruritus, urticaria	not known
Musculoskeletal and connective tissue disorders	muscular weakness, muscle spasms	rare
Renal and urinary disorders	dysuria	uncommon
	pollakisuria	rare
General disorders and administration site conditions	fatigue	common
	asthenia, malaise	uncommon
	oedema, chest discomfort, gait disturbance	rare
Investigations	ALT increased	common
	AST increased, blood alkaline phosphatase increased	uncommon
	red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present, urine output increased	rare

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

Description of selected adverse reactions

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

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

Non-CINV studies

Additional adverse reactions were observed in adult patients treated with aprepitant for post-operative nausea and vomiting (PONV) and a greater incidence than with ondansetron: abdominal pain upper, bowel sounds abnormal, constipation*, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, sub-ileus*, visual acuity reduced, wheezing.

*Reported in patients taking a higher dose of aprepitant.

Fosaprepitant

In an active-controlled clinical study in adult patients receiving HEC, safety was evaluated for 1,143 patients receiving the 1-day regimen of IVEMEND 150 mg compared to 1,169 patients receiving the 3-day regimen of aprepitant. Additionally, in a placebo-controlled clinical trial in adult

patients receiving MEC, safety was evaluated for 504 patients receiving a single dose of IVEMEND 150 mg compared to 497 patients receiving the control regimen.

The safety of the 1-day IV regimen was supported by a pooled analysis of 3 active-controlled clinical studies in 139 paediatric patients (aged 6 months to 17 years) receiving either HEC or MEC and a single dose of IVEMEND at or above the recommended 1-day regimen dose.

The safety of the 3-day IV regimen is supported by a single arm clinical study in 100 paediatric patients (aged 6 months to 17 years) receiving either HEC or MEC and a 3-day regimen of IVEMEND at the recommended dose (see section 4.2). The safety profile of the 3-day IV fosaprepitant regimen in paediatric patients is similar to that of the 1-day fosaprepitant regimen.

The safety profile of fosaprepitant in adult and paediatric patients was generally similar to that observed with aprepitant.

Tabulated list of adverse reactions – fosaprepitant
The following are adverse reactions reported in adult patients receiving fosaprepitant in clinical studies or post-marketing that have not been reported with aprepitant as described above. The frequency categories in the table are based on studies in adults; the observed frequencies in the paediatric studies were similar or lower. Some adverse reactions that are commonly observed in the adult population were not observed in the paediatric studies. Infusion site reactions (ISRs) have been reported with the use of IVEMEND (see section 4.4).

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

Table 6: Tabulated list of adverse reactions – fosaprepitant

System organ class	Adverse reaction	Frequency
Vascular disorders	flushing, thrombophlebitis (predominantly, infusion site thrombophlebitis)	uncommon
Skin and subcutaneous tissue disorders	erythema	uncommon
General disorders and administration site conditions	infusion site erythema, infusion site pain, infusion site pruritus	uncommon
	infusion site induration	rare
	immediate hypersensitivity reactions including flushing, erythema, dyspnoea, anaphylactic reactions/anaphylactic shock	not known
Investigations	blood pressure increased	uncommon

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

4.9 Overdose

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

Aprepitant cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, ATC code: A04AD12.

Fosaprepitant is the prodrug of aprepitant and when administered intravenously is converted rapidly to aprepitant (see section 5.2). The contribution of fosaprepitant to the overall antiemetic effect has not fully been characterised, but a transient contribution during the initial phase cannot be ruled out. Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK_1) receptors. The pharmacological effect of fosaprepitant is attributed to aprepitant.

1-Day Regimen of Fosaprepitant in Adults
Highly Emetogenic Chemotherapy (HEC)
In a randomised, parallel, double-blind, active-controlled study, IVEMEND 150 mg (N=1,147) was compared with a 3-day aprepitant regimen (N=1,175) in adult patients receiving a HEC regimen that included cisplatin (≥ 70 mg/m^2). The fosaprepitant regimen consisted of fosaprepitant 150 mg on Day 1 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1, 8 mg on Day 2, and 8 mg twice daily on Days 3 and 4. The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg daily on Days 2 through 4. Fosaprepitant placebo, aprepitant placebo, and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding (see section 4.2). Although a 32 mg intravenous dose of ondansetron was used in clinical trials, this is no longer the recommended dose. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information.

Efficacy was based on evaluation of the following composite measures: complete response in both the overall and delayed phases and no vomiting in the overall phase. IVEMEND 150 mg was shown to be non-inferior to that of the 3-day regimen of aprepitant. A summary of the primary and secondary endpoints is shown in Table 7.

Table 7: Percent of adult patients receiving Highly Emetogenic Chemotherapy responding by treatment group and phase — Cycle 1

ENDPOINTS[*]	**Fosaprepitant regimen (N =1,106)**[**] **%**	**Aprepitant regimen (N =1,134)**[**] **%**	**Difference**[†] **(95 % CI)**
Complete response[‡]			
Overall[§]	71.9	72.3	-0.4 (-4.1, 3.3)
Delayed phase[§§]	74.3	74.2	0.1 (-3.5, 3.7)
No vomiting			
Overall[§]	72.9	74.6	-1.7 (-5.3, 2.0)

[*]Primary endpoint is bolded.
[**]N: Number of adult patients included in the primary analysis of complete response.
[†]Difference and confidence interval (CI) 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 = 0 to 120 hours post-initiation of cisplatin chemotherapy.
[§§]Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

Moderately Emetogenic Chemotherapy (MEC)

In a randomised, parallel, double-blind, placebo-controlled study, IVEMEND 150 mg (N=502) in combination with ondansetron and dexamethasone was compared with ondansetron and dexamethasone alone (control regimen) (N=498) in adult patients receiving a moderately emetogenic chemotherapy regimen. The fosaprepitant regimen consisted of fosaprepitant 150 mg on Day 1 in combination with oral ondansetron 8 mg for 2 doses and oral dexamethasone 12 mg. On Days 2 and 3, patients in the fosaprepitant group received placebo for ondansetron every 12 hours. The control regimen consisted of fosaprepitant placebo 150 mg IV on Day 1 in combination with oral ondansetron 8 mg for 2 doses and oral dexamethasone 20 mg. On Days 2 and 3, patients in the control group received 8 mg oral ondansetron every 12 hours. Fosaprepitant placebo and dexamethasone placebo (on Day 1) were used to maintain blinding.

The efficacy of fosaprepitant was evaluated based on the primary and secondary endpoints listed in Table 8 and was shown to be superior to the control regimen with regard to complete response in the delayed and overall phases.

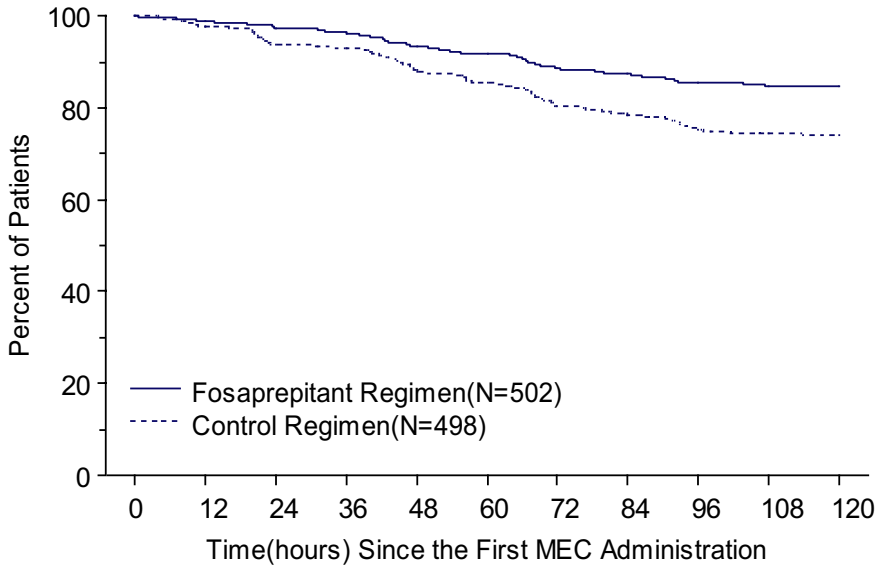
Table 8: Percent of adult patients receiving Moderately Emetogenic Chemotherapy responding by treatment group and phase

ENDPOINTS*	**Fosaprepitant regimen (N =502)** %	**Control regimen (N =498)** %	**P-Value**
Complete response†			
Delayed phase‡	78.9	68.5	< 0.001
Complete response†			
Overall§	77.1	66.9	< 0.001
Acute phase§§	93.2	91	0.184

*Primary endpoint is bolded.
**N: Number of adult patients included in the intention to treat population.
†Complete response = no vomiting and no use of rescue therapy.
‡Delayed phase = 25 to 120 hours post-initiation of chemotherapy.
§Overall = 0 to 120 hours post-initiation of chemotherapy.
§§Acute= 0 to 24 hours post-initiation of chemotherapy.

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

Figure 1: Percent of adult patients receiving Moderately Emetogenic Chemotherapy who remain emesis free over time



Paediatric population
In 3 active-controlled, open-label clinical studies, paediatric patients aged 6 months to 17 years received either highly or moderately emetogenic chemotherapy and a single dose of fosaprepitant at or above the recommended 1-day regimen dose (139 patients) or 3-day regimen (199 patients), in combination with ondansetron with or without dexamethasone.

Paediatric Patients Receiving 1-Day Fosaprepitant Regimen
The efficacy of the 1-day fosaprepitant regimen in paediatric patients was extrapolated from that demonstrated in adults receiving the 1-day fosaprepitant regimen as described in the 1-Day Regimen of Fosaprepitant in Adults subsection.

The efficacy of a 1-day fosaprepitant regimen in paediatric patients is expected to be similar to that of the 1-day adult fosaprepitant regimen.

Paediatric Patients Receiving 3-Day Fosaprepitant Regimen
The efficacy of the 3-day fosaprepitant regimen in paediatric patients was based on that demonstrated in paediatric patients receiving the 3-day oral aprepitant regimen.

The efficacy of a 3-day fosaprepitant regimen in paediatric patients is expected to be similar to that of the 3-day oral aprepitant regimen. See the summary of product characteristics for EMEND capsules and EMEND powder for oral suspension for complete clinical information regarding studies performed with oral aprepitant.

5.2 Pharmacokinetic properties

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant. Plasma concentrations of fosaprepitant are below quantifiable levels within 30 minutes of the completion of infusion.

Aprepitant after fosaprepitant administration
Following a single intravenous 150 mg dose of fosaprepitant administered as a 20-minute infusion to healthy adult volunteers, the mean $AUC_{0-\infty}$ of aprepitant was 35.0 µg•hr/ml and the mean maximal aprepitant concentration was 4.01 µg/ml.

Distribution
Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean volume of distribution at steady state (Vd_{ss}) of aprepitant estimated from a single 150 mg intravenous dose of fosaprepitant is approximately 82 l in humans.

Biotransformation
Fosaprepitant was rapidly converted to aprepitant in *in vitro* incubations with liver preparations from humans. Furthermore, fosaprepitant underwent rapid and nearly complete conversion to aprepitant in S9 preparations from other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple tissues. In humans, fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion.

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

All metabolites observed in urine, faeces and plasma following an intravenous 100 mg [^{14}C]-fosaprepitant dose were also observed following an oral dose of [^{14}C]-aprepitant. Upon conversion of 245.3 mg of fosaprepitant dimeglumine (equivalent to 150 mg fosaprepitant) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

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

The pharmacokinetics of aprepitant is non-linear across the clinical dose range. The terminal half-life of aprepitant following a 150 mg intravenous dose of fosaprepitant was approximately 11 hours. The geometric mean plasma clearance of aprepitant following a 150 mg intravenous dose of fosaprepitant was approximately 73 ml/min.

Pharmacokinetics in special populations
Hepatic impairment: Fosaprepitant is metabolised 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).

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

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21 % and C_{max} decreased by 32 %, relative to healthy subjects. In patients with ESRD

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

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

Paediatric population: As part of a 3-day IV/IV/IV regimen, simulated median AUC_{0-24hr} of aprepitant with median peak plasma concentration (C_{max}) on Day 1 and the median concentrations at the end of Day 1, Day 2 and Day 3 in paediatric patients (6 months to 17 years old) are shown in Table 9.

Table 9: Pharmacokinetic parameters of aprepitant for 3-day IV fosaprepitant regimen in paediatric patients

Population	3-day IV/IV/IV dose	AUC 0-24 hr. (ng*hr/mL)	C_{max} (ng/mL)	C_{24} (ng/mL)	C_{48} (ng/mL)	C_{72} (ng/mL)
12 - 17 years old	115 mg, 80 mg, 80 mg	21,172	2,475	454	424	417
6 - < 12 years old	3 mg/kg, 2 mg/kg, 2 mg/kg	25,901	2,719	518	438	418
2 - < 6 years old		20,568	2,335	336	248	232
6 months – < 2 years old		16,979	1,916	256	179	167

In the 1-day IV fosaprepitant setting, simulated median AUC_{0-24hr} of aprepitant with median peak plasma concentration (C_{max}) on Day 1 and the median concentrations at the end of Day 1, Day 2 and Day 3 in paediatric patients (6 months to < 12 years old) and observed mean AUC_{0-24hr} with median peak plasma concentration (C_{max}) on Day 1 and mean concentrations at the end of Day 1, Day 2 and Day 3 in paediatric patients (12 to 17 years old) are shown in Table 10.

Table 10: Pharmacokinetic parameters of aprepitant for 1-day IV fosaprepitant regimen in paediatric patients

Population	1-day IV dose	AUC 0-24 hr. (ng*hr/mL)	C_{max} (ng/mL)	C_{24} (ng/mL)	C_{48} (ng/mL)	C_{72} (ng/mL)
12 - 17 years old	150 mg	30,400	3,500	735	NR	NR
6 - < 12 years old	4 mg/kg	35,766	3,637	746	227	69.2
2 - < 6 years old		28,655	3,150	494	108	23.5
6 months – <2 years old	5 mg/kg	30,484	3,191	522	112	24.4

NR = Not Reported

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

Relationship between concentration and effect
Positron emission tomography (PET) imaging studies, using a highly specific NK_1 receptor tracer, in healthy young men administered a single intravenous dose of 150 mg fosaprepitant (N=8) demonstrated brain NK_1 receptor occupancy of $\geq$ 100 % at $T_{max,}$ and 24 hours, $\geq$ 97 % at 48 hours, and between 41 % and 75 % at 120 hours, following dosing. Occupancy of brain NK_1 receptors, in this study, correlate well with aprepitant plasma concentrations.

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 and development.

Carcinogenic potential in rodents was only investigated with orally administered aprepitant. However, it should be noted that the value of the toxicity studies carried out with rodents, rabbits and monkeys, including the reproduction toxicity studies, are limited since systemic exposures to fosaprepitant and aprepitant were only similar or even lower than therapeutic exposure in adult humans. In the performed safety pharmacology and repeated dose toxicity studies with dogs, fosaprepitant C_{max} and aprepitant AUC values were up to 3 times and 40 times, respectively, higher than clinical values.

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

In laboratory animals, fosaprepitant in non-commercial formulations caused vascular toxicity and haemolysis at concentrations below 1 mg/ml and higher, dependent on the formulation. In human washed blood cells also evidence of haemolysis was found with non-commercial formulations at fosaprepitant concentrations of 2.3 mg/ml and higher, although tests in human whole blood were negative. No haemolysis was found with the commercial formulation up to a fosaprepitant concentration of 1 mg/ml in human whole blood and washed human erythrocytes.

In rabbits, fosaprepitant caused initial transient local acute inflammation following paravenous, subcutaneous and intramuscular administration. At the end of the follow-up period (post-dose day 8), up to slight local subacute inflammation was noted following paravenous and intramuscular administration and additional up to moderate focal muscle degeneration/necrosis with muscle regeneration following intramuscular administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate (E386)
Polysorbate 80 (E433)
Lactose anhydrous
Sodium hydroxide (E524) (for pH adjustment) and/or
Hydrochloric acid diluted (E507) (for pH adjustment)

6.2 Incompatibilities

IVEMEND is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Hartman's and lactated Ringer's solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

2 years.

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml Type I clear glass vial with a chlorobutyl or bromobutyl rubber stopper and an aluminium seal with a grey plastic flip off cap.

Pack sizes: 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

IVEMEND must be reconstituted and then diluted prior to 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 and final concentration of 1 mg/ml**. Gently invert the bag 2-3 times.

4. Determine the volume to be administered from this prepared infusion bag, based on the recommended dose (see section 4.2).

   Adults
   The entire volume of the prepared infusion bag (150 ml) should be administered.

Paediatrics
In patients 12 years and older, the volume to be administered is calculated as follows:

- Volume to administer (ml) equals the recommended dose (mg)

In patients 6 months to less than 12 years, the volume to be administered is calculated as follows:

- Volume to administer (ml) = recommended dose (mg/kg) x weight (kg)
  - **Note: Do not exceed maximum doses (see section 4.2).**

5. If necessary, for volumes less than 150 ml, the calculated volume can be transferred to an appropriate size bag or syringe prior to administration by infusion.

The appearance of the reconstituted solution is the same as the appearance of the diluent.

The reconstituted and diluted medicinal product should be inspected visually for particulate matter and discoloration before administration.

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

The medicinal product must not be reconstituted or mixed with solutions for which physical and chemical compatibility has not been established (see section 6.2).

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/07/437/003
EU/1/07/437/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 11 January 2008
Date of latest renewal: 12 November 2012

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 150 mg

1. NAME OF THE MEDICINAL PRODUCT

IVEMEND 150 mg powder for solution for infusion
fosaprepitant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant, which corresponds to 130.5 mg of aprepitant. After reconstitution and dilution 1 ml of solution contains 1 mg fosaprepitant (1 mg/ml).

3. LIST OF EXCIPIENTS

Disodium edetate, polysorbate 80, lactose anhydrous, NaOH and/or HCl diluted (for pH adjustment).
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

powder for solution for infusion
1 vial
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Use of oral aprepitant not required
Read the package leaflet before use.
Intravenous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

After reconstitution and dilution: 24 hours at 25°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/437/003 1 x 1 vial
EU/1/07/437/004 1 x 10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IVEMEND 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL 150 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IVEMEND 150 mg powder for solution for infusion
fosaprepitant
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

IVEMEND 150 mg powder for solution for infusion
fosaprepitant

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IVEMEND is and what it is used for

IVEMEND contains the active substance fosaprepitant which is converted to aprepitant in your body. It belongs to a group of medicines called "neurokinin 1 (NK_1) receptor antagonists". The brain has a specific area that controls nausea and vomiting. IVEMEND works by blocking signals to that area, thereby reducing nausea and vomiting. IVEMEND is used in adults, adolescents, and children aged 6 months or older **in combination with other medicines** to prevent nausea and vomiting caused by chemotherapy (cancer treatment) that is a strong or moderate trigger of nausea and vomiting.

2. What you need to know before you use IVEMEND

Do not use IVEMEND
- if you are allergic to fosaprepitant, aprepitant, or to polysorbate 80 or any of the other ingredients of this medicine (listed in section 6).
- with medicines containing pimozide (used to treat psychiatric illnesses), terfenadine and astemizole (used for hay fever and other allergic conditions), cisapride (used for treating digestive problems). Tell your doctor if you are taking these medicines since the treatment must be modified before you start using IVEMEND.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before using IVEMEND.

Before treatment with this medicine, tell your doctor if you have liver disease because the liver is important in breaking down the medicine in the body. Your doctor may therefore have to monitor the condition of your liver.

Children and adolescents
Do not give IVEMEND to children under 6 months of age or who weigh less than 6 kg, because it has not been studied in this population.

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

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

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

Tell your doctor about any other medicines or herbal medicines you are taking, have recently taken, or might take.

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

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

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

Driving and using machines
It should be taken into account that some people get dizzy and get sleepy after using IVEMEND. If you get dizzy or get sleepy, avoid driving or using machines after using this medicine (see 'Possible side effects').

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

3. How to use IVEMEND

In adults (18 years of age and older), the recommended dose of IVEMEND is 150 mg fosaprepitant on Day 1 (day of chemotherapy).

In children and adolescents (6 months to 17 years of age), the recommended dose of IVEMEND is based on the patient's age and weight. Depending on the chemotherapy treatment, there are two ways IVEMEND may be given:

IVEMEND is given only on Day 1 (single day of chemotherapy)

IVEMEND is given on Day 1, 2, and 3 (single or multiple days of chemotherapy)

- Oral formulations of aprepitant may be prescribed on Days 2 and 3 instead of IVEMEND.

The powder is reconstituted and diluted before use. The solution for infusion is given to you by a health care professional, such as a doctor or nurse, via an intravenous infusion (a drip) approximately 30 minutes before you start the chemotherapy treatment in adults or 60 – 90 minutes before you start the chemotherapy treatment in children and adolescents. Your doctor may ask you to take other medicines including a corticosteroid (such as dexamethasone) and a '5-HT_3 antagonist' (such as ondansetron) for preventing nausea and vomiting. Check with your doctor or pharmacist if you are not sure.

4. Possible side effects

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

Stop taking IVEMEND and see a doctor immediately if you notice any of the following side effects, which may be serious, and for which you may need urgent medical treatment:

- Hives, rash, itching, difficulty breathing or swallowing, or a serious decrease of blood pressure (frequency not known, cannot be estimated from the available data); these are signs of a serious allergic reaction.
- Infusion site reactions (ISR) at or near the infusion site. Most severe ISR have happened with a certain type of chemotherapy medicine that can burn or blister your skin (vesicant) with side effects, including pain, swelling and redness. Death of skin tissue (necrosis) has happened in some people getting this type of chemotherapy medicine.

Other side effects that have been reported are listed below.

Common side effects (may affect up to 1 in 10 people) are:

- constipation, indigestion,
- headache,
- tiredness,
- loss of appetite,
- hiccups,
- increased amount of liver enzymes in your blood.

Uncommon side effects (may affect up to 1 in 100 people) are:

- dizziness, sleepiness,
- acne, rash,
- anxiousness,
- burping, nausea, vomiting, heartburn, stomach pain, dry mouth, passing wind,
- increased painful or burning urination,
- weakness, generally feeling unwell,
- reddening of the face/skin, hot flush,
- fast or irregular heartbeats, blood pressure increased,
- fever with increased risk of infection, lowering of red blood cells,

- infusion site pain, infusion site redness, infusion site itching, infusion site vein inflammation.

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

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

5. How to store IVEMEND

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

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The first 2 numbers indicate the month; the next 4 numbers indicate the year.

Store in a refrigerator (2 °C - 8 °C).

The reconstituted and diluted solution is stable for 24 hours at 25 °C.

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

6. Contents of the pack and other information

What IVEMEND contains
- The active substance is fosaprepitant. Each vial contains fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant. After reconstitution and dilution 1 ml of solution contains 1 mg fosaprepitant (1 mg/ml).
- The other ingredients are: disodium edetate (E 386), polysorbate 80 (E 433), lactose anhydrous, sodium hydroxide (E 524) (for pH adjustment) and/or hydrochloric acid diluted (E 507) (for pH adjustment).

What IVEMEND looks like and contents of the pack
IVEMEND is a white to off-white powder for solution for infusion.

The powder is contained in a clear glass vial with a rubber stopper and an aluminium seal with a grey plastic flip off cap.

Each vial contains 150 mg of fosaprepitant. Pack sizes: 1 or 10 vials.

Not all pack sizes may be marketed.

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

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

The following information is intended for healthcare professionals only:

Instructions of how to reconstitute and dilute IVEMEND 150 mg

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 and final concentration of 1 mg/ml**. Gently invert the bag 2-3 times (see 'How to use IVEMEND').

4. Determine the volume to be administered from this prepared infusion bag, based on the recommended dose (see Summary of Product Characteristic (SmPC), section 4.2).

   Adults
   The entire volume of the prepared infusion bag (150 ml) should be administered.

   Paediatrics
   In patients 12 years and older, the volume to be administered is calculated as follows:
   - Volume to administer (ml) equals the recommended dose (mg)

   In patients 6 months to less than 12 years, the volume to be administered is calculated as follows:
   - Volume to administer (ml) = recommended dose (mg/kg) x weight (kg)
     - **Note: Do not exceed maximum doses (see Summary of Product Characteristic (SmPC), section 4.2).**

5. If necessary, for volumes less than 150 ml, the calculated volume can be transferred to an appropriate size bag or syringe prior to administration by infusion.

The reconstituted and diluted final solution is stable for 24 hours at 25 °C.

Parenteral medicines should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

The appearance of the reconstituted solution is the same as the appearance of the diluent.

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

The medicinal product must not be reconstituted or mixed with solutions for which physical and chemical compatibility has not been established (see Summary of Product Characteristic (SmPC), section 6.2).