SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FOSAP (Fosaprepitant Dimeglumine for Injection 150 mg/vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial contains 245.3 mg Fosaprepitant Dimeglumine is equivalent to 150 mg Fosaprepitant.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Injection

A white to off white lyophilized cake or 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.

Fosaprepitant 150 mg is given as part of a combination therapy.

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. Fosaprepitant should be administered in conjunction with a corticosteroid and a 5-HT3 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
Fosaprepitant	150 mg intravenously	none	none	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT3 antagonists	Standard dose of 5-HT3 antagonists. See the product information for the selected 5-HT3 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
Fosaprepitant	150 mg intravenously
Dexamethasone	12 mg orally
5-HT3 antagonists	Standard dose of 5-HT3 antagonists. See the product information for the selected 5-HT3 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 Fosaprepitant, to be administered with a 5-HT3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemo therapy regimens of Highly Emetogenic Chemotherapy (HEC) or Moderately Emetogenic Chemotherapy (MEC). 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 3.

Dosing for Single or Multi-Day Chemotherapy Regimens

For paediatric patients receiving single or multi-day regimens of HEC or MEC, administer Fosaprepitant as an intravenous infusion through a central venous catheter on Days 1, 2, and 3.

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

	Population	**Day 1**
Fosaprepitant *	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-HT3 antagonist	All paediatric patients	See selected 5-HT3 antagonist prescribing information for the recommended dosage

* For paediatric patients 12 years and older, administer Fosaprepitant intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy. For paediatric patients less than 12 years, administer Fosaprepitant 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 Fosaprepitant in infants below 6 months of age have not been established. No data are available.

General

Efficacy data in combination with other corticosteroids and 5-HT3 antagonists are limited. For additional information on the co-administration with corticosteroids.

Refer to the Summary of Product Characteristics of co-administered 5-HT3 antagonist medicinal products.

Special populations

Elderly (≥65 years)

No dose adjustment is necessary for the elderly.

Gender

No dose adjustment is necessary based on gender.

- *Renal impairment*

No dose adjustment is necessary for patients with renal impairment or for patients with end stage renal disease undergoing haemodialysis.

- *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. Fosaprepitant should be used with caution in these patients.

Method of administration

Fosaprepitant 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 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. Do not administer Fosaprepitant as a bolus injection or undiluted solution.
For instructions on reconstitution and dilution of the medicinal product before administration.

4.3 Contraindications

Hypersensitivity to the active substance or to polysorbate 80 or any of the other excipients mentioned in list of excipients section.

Co-administration with pimozide, terfenadine, astemizole or cisapride.

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. Fosaprepitant should be used with caution in these patients.

CYP3A4 interactions

Fosaprepitant should be used with caution in patients receiving concomitant active substances that are metabolized primarily through CYP3A4 and with a narrow therapeutic range, such as ciclosporin, tacrolimus, sirolimus, everolimus alfentanil, ergot alkaloid derivatives, fentanyl, and quinidine. 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 Normalized Ratio (INR) should be monitored closely for 14 days following the use of Fosaprepitant.

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 2months following the use of Fosaprepitant.

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 Fosaprepitant. 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.

Fosaprepitant should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion. Fosaprepitant should not be administered intramuscularly or subcutaneously. 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 1mmol 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 Fosaprepitant with other medicinal products in paediatric patients are based upon adult data from Fosaprepitant and aprepitant studies.

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 ofCYP3A4 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. 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.

Corticosteroids

Dexamethasone*:* The oral dexamethasone dose should be reduced by approximately 50 % when co-administered with Fosaprepitant. Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased theAUC0-24hr 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, Fosaprepitant 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. 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 Fosaprepitant.

Midazolam

Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the AUC0-∞ 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 and4. 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 viaCYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicinal products With Fosaprepitant.

Diltiazem

Interaction studies with Fosaprepitant 150 mg and diltiazem have not been conducted; however, the following study with100 mg of Fosaprepitant should be considered when using Fosaprepitant 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 Fosaprepitant 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 Fosaprepitant.

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 Fosaprepitant for the prevention of chemotherapy induced nausea and vomiting.

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 2months following the use of Fosaprepitant.

5-HT3 antagonists

Interaction studies with Fosaprepitant 150 mg and 5-HT3 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 Fosaprepitant 150 mg and 5-HT3 antagonists.

Effect of other medicinal products on the pharmacokinetics of aprepitant resulting from administration of fosaprepitant150 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. 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 with100 mg of Fosaprepitant should be considered when using Fosaprepitant 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 Pregnancy, lactation and Special population

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 2months following the last dose of Fosaprepitant.

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. The potential effects on reproduction of alterations in neurokinin regulation are unknown. Fosaprepitant 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 Fosaprepitant.

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.

4.7 Effects on ability to drive and use machines

Fosaprepitant may have minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of Fosaprepitant.

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 371healthy 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.

Fosaprepitant

In an active-controlled clinical study in adult patients receiving HEC, safety was evaluated for 1,143 patients receiving the1-day regimen of Fosaprepitant 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 Fosaprepitant 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 139paediatric patients (aged 6 months to 17 years) receiving either HEC or MEC and a single dose of Fosaprepitant 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 pediatric patients (aged 6 months to 17 years) receiving either HEC or MEC and a 3-day regimen of Fosaprepitant at the recommended dose. The safety profile of the 3-day IV Fosaprepitant regimen in pediatric patients is similar to that of the 1-dayfosaprepitant regimen.

The safety profile of Fosaprepitant in adult and pediatric 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 pediatric studies were similar or lower. Some adverse reactions that are commonly observed in the adult population were not observed in the pediatric studies. Infusion site reactions (ISRs) have been reported with the use of Fosaprepitant.

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 4: 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

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: Antiemetic and antinauseants

ATC code: A04AD12.

Fosaprepitant is the prodrug of aprepitant and when administered intravenously is converted rapidly to aprepitant. The contribution of Fosaprepitant to the overall antiemetic effect has not fully been characterized, 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 (NK1) receptors. The pharmacological effect of Fosaprepitant is attributed to aprepitant.1-Day Regimen of Fosaprepitant in Adults.

Highly Emetogenic Chemotherapy (HEC)

In a randomized, parallel, double blind, active-controlled study, Fosaprepitant 150 mg (N=1,147) was compared with a 3-dayaprepitant regimen (N=1,175) in adult patients receiving a HEC regimen that included cisplatin ($\geq$ 70 mg/m^2). The Fosaprepitant regimen consisted of Fosaprepitant 150 mg on Day 1 in combination with ondansetron 32 mg IV on Day 1and 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. 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-HT3 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. Fosaprepitant 150 mg was shown to be non-inferior to that of the 3-dayregimen of aprepitant. A summary of the primary and secondary endpoints is shown in Table 5.

Table 5: 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, Fosaprepitant 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 12hours. 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 6 and was shown to be superior to the control regimen with regard to complete response in the delayed and overall phases.

Table 6 : 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.

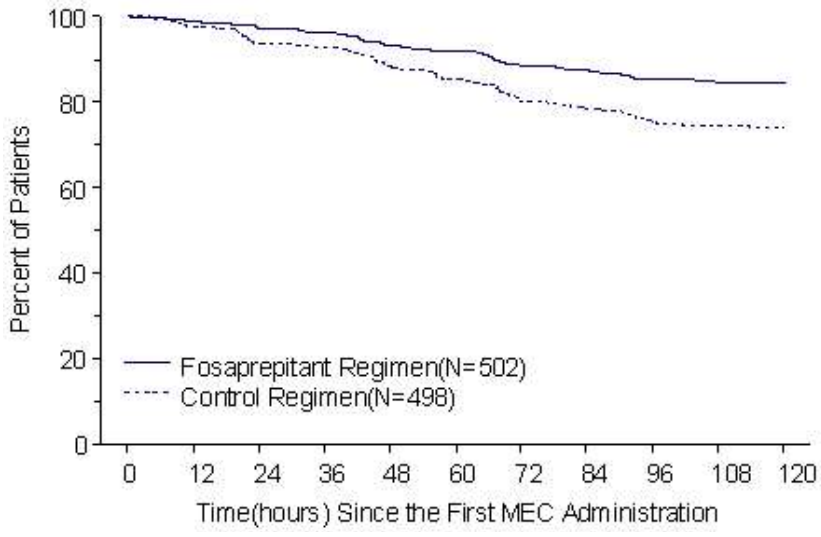
‡ Delayed phase = 25 to 120 hours post-initiation of chemotherapy.

§ 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.

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 4.01µg/ml.

Distribution

Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean volume of distribution at steady state (Vdss) 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 within30 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 [14C]- 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 andCYP2C19.

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 [14C]-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 AUC0-∞ of total aprepitant (unbound and protein bound) decreased by 21 %and Cmax decreased by 32 %, relative to healthy subjects. In patients with ESRD undergoing haemodialysis, the AUC0-∞ of total aprepitant decreased by 42 % and Cmax 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 AUC0-24hr of aprepitant with median peak plasma concentration (Cmax) 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 7.

Table 7: 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 8.

Table 8: 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) suggeststhat 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 NK1-receptor tracer, in healthy young men administered a single intravenous dose of 150 mg Fosaprepitant (N=8) demonstrated brain NK1 receptor occupancy of ≥100 % at Tmax, and 24 hours, ≥ 97 % at 48 hours, and between 41 % and 75 % at 120 hours, following dosing. Occupancy of brain NK1 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, Geno toxicity (including invitro 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 Cmax 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 Ley dig 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 para venous, subcutaneous and intramuscular administration. At the end of the follow-up period (post-dose day 8), up to slight local sub-acute inflammation was noted following para venous 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:

Edetate Disodium, Lactose anhydrous (DTHV), Polysorbate 80, Sodium hydroxide, Hydrochloric acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Fosaprepitant Dimeglumine for injection vials must be refrigerated, store at 2°C-8°C (36°F-46°F).

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

6.5 Nature and contents of pack's

1x1 vial (150mg/vial)

6.6 Instructions for use, handling and disposal

Not applicable.

7. SUPPLIER

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8. Registration Number

Not applicable

9. Date of Publication of this Package Insert

Not applicable