21001155

FOSAPREPITANT
℞ FOSAP

FOSAPREPITANT
℞ FOSAP

150 mg Lyophilized Powder for Solution for IV Infusion

Antiemetic

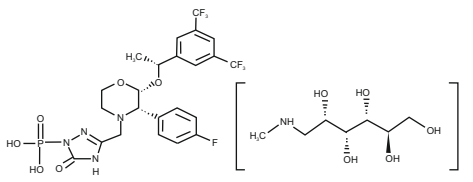
FORMULATION:

Each vial contains: Fosaprepitant Dimeglumine ....245.3 mg (equivalent to Fosaprepitant 150 mg)

DRUG DESCRIPTION

White to off white lyophilized cake or powder.

Fosaprepitant Dimeglumine is described chemically as i)1-Deoxy-1-(methylamino)-D-glucitol [3-[[(2R,3S)-2-[(1R)-1-[3,5 -bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl] methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]-phosphonate (2:1) (salt). The molecular formula is $C_{23}H_{22}F_7N_4O_8P.2C_7H_{17}NO_5$ and the molecular weight is 1004.83 The chemical structure of Fosaprepitant Dimeglumine is:



Fosaprepitant Dimeglumine contain the following inactive ingredients: Disodium Edetate, Lactose anhydrous, Polysorbate 80, Sodium hydroxide, Hydrochloric acid, Water for Injection.

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.

POSOLOGY AND METHOD OF ADMINISTRATION

- **RECOMMENDED DOSE & ROUTE 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 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. Do not administer Fosaprepitant Dimiglumine as a bolus injection or undiluted solution.

It should be reconstituted with 5 mL of 0.9% w/v Sodium chloride injection (primary dilution) then diluted with 145 mL of 0.9% w/v Sodium chloride Injection (secondary dilution) to get a final concentration of 1 mg/mL.

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

CONTRAINDICATIONS

Hypersensitivity to the active substance or to polysorbate 80 or any of the other excipients

Co-administration with pimozide, terfenadine, astemizole or cisapride

DRUG INTERACTIONS

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 Dimeglumine 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 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. 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 cyclosporine, 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 the AUC0-24hr 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 Dimeglumine 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 metabolized primarily or partly by CYP3A4. Post-marketing 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. cyclosporine, 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 Dimeglumine.

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 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 Fosaprepitant Dimeglumine.

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 Fosaprepitant Dimeglumine 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 Dimeglumine 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 Dimeglumine

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 Dimeglumine 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 2 months following the use of fosaprepitant.

5-HT$_3$ 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 Dimeglumine 150 mg and 5-HT3 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. 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 Fosaprepitant Dimeglumine 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.

WARNINGS AND PRECAUTIONS

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 Dimeglamine should be used with caution in these patients

CYP3A4 interactions

Fosaprepitant Dimeglumine 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 cyclosporine, 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 Normalised 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 2 months 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 Dimeglumine. 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 Dimeglumine should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion. Fosaprepitant Dimeglumine 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

Adverse 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 199 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 postmarketing 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).

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
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
	asthaenia, 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.

Additional adverse reactions were observed in adult patients treated with aprepitant for postoperative 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 Fosaprepitant Dimeglumine 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 Dimeglumine 150 mg compared to 497 patients receiving the control regimen.

In a pooled analysis of 3 active-controlled clinical studies in paediatric patients (aged 6 months to 17 years) receiving either HEC or MEC and a single dose of Fosaprepitant Dimeglumine at or above the recommended 1-day regimen dose, safety was evaluated for 139 patients receiving the 1-day regimen of Fosaprepitant Dimeglumine. In the same analysis, safety was evaluated for 199 patients receiving either HEC or MEC and a single dose of Fosaprepitant Dimeglumine at or above the recommended 3-day regimen of Fosaprepitant Dimeglumine. Safety data following the administration of the 3-day IV/oral/oral regimen were also included.

No data are available following the administration of a 3-day IV fosaprepitant regimen in paediatric patients. The safety profile of the 3-day IV fosaprepitant regimen in paediatric patients is expected to be similar to that of the 1-day fosaprepitant regimen as the low daily trough levels do not significantly increase the exposures on subsequent days.

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 postmarketing 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 Fosaprepitant Dimeglumine.

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).

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 FDA at www.fda.gov.ph..

- **PREGNANCY, LACTATION AND FERTILITY**

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

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 Dimeglumine should not be used during pregnancy unless clearly necessary.

Size : 250 x 435 mm
Colour : Black
Note: Pharma code position and Orientation are tentative, will be changed based on folding size.

21001155
FOSAPREPITANT
℞ FOSAP

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 Dimeglumine.

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.

- **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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 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 (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 Dimeglumine 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/m2). 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. 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 Dimeglamine 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

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 randomized, parallel, double-blind, placebo-controlled study, Fosaprepitant Dimeglumine 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.

Percent of adult patients receiving Highly 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.

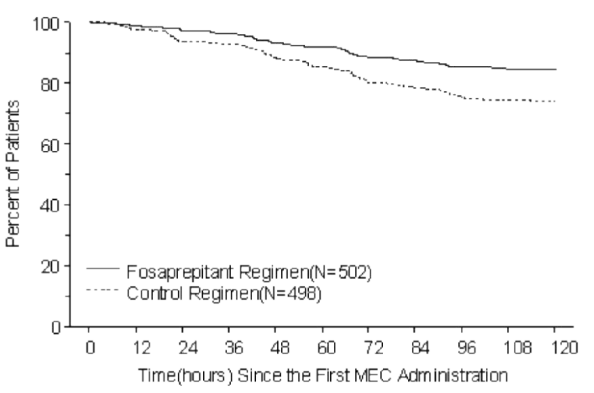
§Overall = 0 to 120 hours post-initiation of chemotherapy.

§§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 aprepitant capsules and aprepitant powder for oral suspension for complete clinical information regarding studies performed with oral aprepitant.

Pharmacokinetics

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 AUC0-∞ 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 (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 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 [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 and CYP2C19.

All metabolites observed in urine, faeces and plasma following an intravenous 100 mg [14C]-fosaprepitant dose were also observed following an oral dose of [14C]-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 metabolized in various extrahepatic tissues; therefore hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant. Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a clinically relevant extent. No dose adjustment is necessary for patients with mild hepatic impairment. Conclusions regarding the influence of moderate hepatic impairment (Child-Pugh class B) on aprepitant pharmacokinetics cannot be drawn from available data. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh class C).

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

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

Population	3-dayIV/IV/IV dose	$AUC_{0\text{-}24\,hr}$ (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	21172	2475	454	424	417
6 - < 12 years old	3 mg/kg, 2 mg/kg, 2 mg/kg	25901	2719	518	438	418
2 - < 12 years old		20568	2335	336	248	232
6 months – < 2 years old		16979	1916	256	179	167

In the 1-day IV fosaprepitant setting, 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 < 12 years old) and observed mean AUC0-24hr with median peak plasma concentration (Cmax) 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

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

Population	1-day IV dose	$AUC_{0\text{-}24\,hr}$ (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	30400	3500	735	NR*	NR*
6 - < 12 years old	4 mg/kg	35766	3637	746	227	69.2
2 - < 6 years old		28655	3150	494	108	23.5
6 months – <2 years old	5 mg/kg	30484	3191	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 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.

- **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.

Availability:
10 mL -capacity USP Type I tubular glass vial sealed with grey bromobutyl rubber stopper and flip -off seal (Box of 1's).

STORAGE CONDITION
Store at temperatures between 2 to 8°C.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction

Manufactured by:
ASPIRO PHARMA LIMITED
Sy. No. 321, Biotech Park, Phase-III,
Karkapatla Village, Markook Mandal,
Siddipet District - 502281, Telangana State, INDIA.

Imported and Distributed by:
CAMBER PHARMACEUTICALS, INC.
Unit 503-A ITC Bldg., 337 Sen. Gil Puyat Avenue,
Bel-Air, Makati City, Philippines.

Registration Number: DR-XY48536
Date of First Authorization: Dec 2022
Date of Revision of Package Insert: May 2023