FOSAPREPITANT DIMEGLUMINE FOR INJECTION 150 MG

Zemecon-150

COMPOSITION :

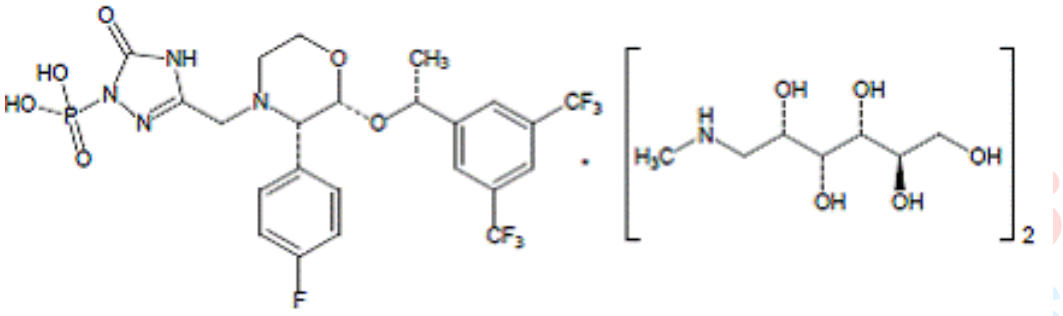
Each vial contains :

Fosaprepitant Dimeglumine	245.3 mg.
Eq. to Fosaprepitant	150 mg.
Excipients	q.s.

(As sterile freeze-dried powder for reconstitution).

DESCRIPTION

Fosaprepitant dimeglumine for Injection is a sterile, lyophilized prodrug of aprepitant, a substance P/neurokin in-1 (NK1) receptor antagonist, and is chemically described as 1- Deoxy-1- (methylamino)-D-glucitol[3-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyllethoxy]-3-(4- fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl] phosphonate(2:1) (salt). Its empirical formula is $C_{23}H_{22}F_7N_4O_6P$. $2(C_7H_{17}NO_5)$and its structural formula is:



Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83. It is freely soluble in water. Each vial of Fosaprepitant for Injection 150 mg for intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Fosaprepitant dimeglumine hereafter will be referred to as fosaprepitant.

Clinical Pharmacology

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK,) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion. Upon conversion of 188 mg of fosaprepitant dimeglumine (equivalent to 115 mg fosaprepitant free acid) to aprepitant, 18.3 mg of phosphoric acid and 73 mg of meglumine are liberated. Upon conversion of 245.3 mg of fosaprepitant dimeglumine (equivalent to 150 mg fosaprepitant free acid) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

Mechanisam of Action

Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK,) receptors. Aprepitant has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV). Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

Pharmacodynamics:

NK, Receptor Occupancy

In two single-blind, multiple-dose, randomized, and placebo control studies, healthy young men received oral aprepitant doses of 10 mg (N=2), 30 mg (N=3), 100 mg (N=3) or 300 mg (N=5) once daily for 14 days with 2 or 3 subjects on placebo. Both plasma aprepitant concentration and NK, receptor occupancy in the corpus striatum by positron emission tomography were evaluated, at predose and 24 hours after the last dose. At aprepitant plasma concentrations of -10 ng/mL and -100 ng/mL, the NK, receptor occupancies were -50% and -90%, respectively. The oral aprepitant regimen for CINV produces mean trough plasma aprepitant concentrations >500 ng/mL, which would be expected to, based on the fitted curve with the Hill equation, result in >95% brain NK, receptor occupancy. However, the receptor occupancy for either CINV or PONY dosing regimen has not been determined. In addition, the relationship between NK, receptor occupancy and the clinical efficacy of aprepitant has not been established.

Cardiac Electrophysiologv In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant had no effect on the QTc interval. Pharmacokinetics Following a single, intravenous 150-mg dose of fosaprepitant administered as a 20-minute infusion

Metabolism

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

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of rq-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have *been* identified in human plasma.

Excretion

Following administration of a single intravenous 100-mg dose of [>C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Specific Populations

Gender

Following oral administration of a single dose of aprepitant, the AUC„,„„ and C,,, are 14% and 22% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T„®, occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Geriatric

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{03„„}$, of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (565 years) relative to younger adults. The C,,„ was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment is necessary in elderly patients.

Race

Following oral administration of a single dose of aprepitant, the AUC„,,„, and C„ are approximately 42% and 29% higher in Hispanics as compared with Caucasians. The AUC„,,,„, and C„„ are 62% and 41% higher in Asians as compared to Caucasians. There was no difference in AUC„,„, or C„®, between Caucasians and Blacks. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on race.

Body Mass Index (BMI)

For every 5 kg/n-1[2] increase in BMI,° ' AUC, and C of aprepitant decrease by 11%. BMI of subjects

in the analysis ranged from 18 kg/m to 36 kg/m[2] . This change is not considered clinically

meaningful. No dosage adjustment is necessary based on BMI.

Hepatic Insufficiency

Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant.

Following administration of a single 125-mg dose of oral aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic impairment (Child-Pugh score 5 to 6), the $AUC_{0\text{-}24hr}$, of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the AUC,,,„„, of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in $AUC_{0\text{-}24hr}$, are not considered clinically meaningful; therefore, no dosage adjustment is necessary in patients with mild to moderate hepatic impairment.

There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score >9)

Renal Insufficiency

A single 240-mg dose of oral aprepitant was administered to patients with severe renal impairment (creatinine clearance <30 mUmin/1.73 m' as measured by 24-hour urinary creatinine clearance) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal impairment, the AUC„, of total aprepitant (unbound and protein bound) decreased by 21% and Cmax decreased by 32%, relative to healthy subjects (creatinine clearance >80 mUmin estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the AUC„„„ of total aprepitant decreased by 42% and C_{am}, decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis 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 dosage adjustment is necessary for patients with renal impairment or for patients with ESRD undergoing hemodialysis.

INDICATIONS AND USAGE

Fosaprepitant for Injection is a substance P/neurokinin-1 (NK,) receptor antagonist indicated in adults for use in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

DOSAGE AND ADMINISTRATION:

Prevention of Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy(HEC)

Fosaprepitant for Injection 150 mg (Single Dose Regimen of Fosaprepitant):

Fosaprepitant for Injection 150 mg is administered intravenously on Day 1 only as an infusion over **20.30 minutes** initiated approximately 30 minutes prior to chemotherapy. No capsules of Fosaprepitant are administered on Days 2 and 3. Fosaprepitant for Injection should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in Table 1. The recommended dosage of dexamethasone with Fosaprepitant for Injection 150 mg differs from the recommended dosage of dexamethasone with Fosaprepitant for Injection 115 mg on Days 3 and 4.

Table 1: Recommended dosing (3-Day Dosing Regimen of Fosaprepitant for Injection 150 mg) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant for Injection 150 mg	150 mg intravenous	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally twice	8 mg orally twice
Ondansetron	32 mg intravenous	none	none	none

Dexamethasone should be administered 30 minutes prio to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone accounts for drug interactions.

Ondansetron should be administered 30 minutes prior to chemotherapy treatment on Day

Preparation of Fosaprepitant for Injection 150 mg

Table 2: Preparation Instructions for Fosaprepitant for Injection 150 mg

Step 1	Aseptically withdraw 5 mL of 0.9% Sodium Chloride for injection IP from 500 mL infusion bag. Aseptically inject 5 mL 0.9% Sodium Chloride for Injection IP (normal
Step	Aseptically prepare an infusion bag filled with **145 mL**
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing **145 mL** of
Step	Gently invert the bag 2-3 times.

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

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

CONTRAINDICATIONS

Hypersensitivity

Fosaprepitant for Injection is contraindicated in patients who are hypersensitive to Fosaprepitant for Injection, aprepitant, polysorbate 80 or any other components of the product. Known hypersensitivity reactions include: flushing, erythema, dyspnea, and anaphylactic reactions.

Concomitant Use with Pimozide or Cisapride

Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, do not use fosaprepitant concurrently with pimozide or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

WARNINGS AND PRECAUTIONS

CYP3A4 Interactions

Fosaprepitant is rapidly converted to aprepitant, which is a moderate inhibitor of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Fosaprepitant should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant or fosaprepitant could result in elevated plasma concentrations of these concomitant medications. When fosaprepitant is used concomitantly with another CYP3A4 inhibitor, aprepitant plasma concentrations could be elevated. When aprepitant is used concomitantly with medications that induce CYP3A4 activity,aprepitant plasma concentrations could be reduced, and this

may result in decreased efficacy of aprepitant. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, the oral aprepitant regimen was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. In separate pharmacokinetic studies, no clinically significant change in docetaxel or vinorelbine pharrnacokinetics was observed when the oral aprepitant regimen was coadministered.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine,vincristine,or ifosfamide,particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied

Hypersensitivity Reactions

Isolated reports of immediate hypersensitivity reactions including flushing, erythema, dyspnea, and anaphylaxis have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. Reinitiation of the infusion is not recommended in patients who experience these symptoms during first-time use.

Coadministration with Warfarin (a CYP2C9 substrate)

Coadministration of fosaprepitant or aprepitant with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

Coadministration with Hormonal Contraceptives

Upon coadministration with fosaprepitant or aprepitant, the efficacy of hormonal contraceptives may be reduced during and for 28 days following the last dose of either fosaprepitant or aprepitant. Alternative or back-up methods of contraception should be used during treatment with and for 1 month following the last dose of fosaprepitant or aprepitant.

Chronic Continuous Use

Chronic continuous use of Fosaprepitent for Injection for prevention of nausea and vomiting is not recommended because it has not been studied; and because the drug interaction profile may change during chronic continuous use.

OVERDOSAGE

There is no specific information on the treatment of over dosage with fosaprepitant or aprepitant. In the event of overdose, fosaprepitant and/or oral aprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective. Aprepitant cannot be removed by hemodialysis. Thirteen patients in the randomized controlled trial of Fosaprepitent for Injection received both fosaprepitant 150 mg and at least one dose of oral aprepitant, 125 mg or 80 mg. Three patients reported adverse reactions that were similar to those experienced by the total study population.

STORAGE

Store at a temperature between 2°C to 8°C.

Keep out of reach of children.

PACKAGING INFORMATION

One 150 mg single dose glass vial: White to off-white lyophilized solid. Supplied as 1 vial per carton.