Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

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Fosaprepitant Dimeglumine For Injection 150mg/Vial

Biocon

Fosaport® फोसापोर्ट

COMPOSITION
Each vial contains:
Fosaprepitant Dimeglumine 245.3 mg
Equivalent to Fosaprepitant 150 mg

PHARMACEUTICAL FORM
Lyophilized powder for solution for injection.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Antiemetics and antinauseants, other antiemetics.
ATC code: A04AD12

Clinical Efficacy Studies
Fosaprepitant is the prodrug and it rapidly gets converted to aprepitant. Its antiemetic effects are attributable to aprepitant.
Aprepitant
To characterize treatment response of aprepitant in patients with various malignancies (e.g., breast, gastrointestinal, genitourinary, and lung), a pooled analysis of patient-level data from 4 large randomized trials were performed (N=2813). The patients were treated with either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) regimens. Patients receiving an antiemetic regimen containing aprepitant, ondansetron, and dexamethasone were compared with patients receiving an active-control antiemetic regimen containing ondansetron plus dexamethasone. In all tumor types analyzed, complete responses were observed in a higher proportion of HEC-treated patients receiving aprepitant compared with active-control patients. For MEC-treated patients, complete response rates were also higher for aprepitant patients than active control patients. The proportion of patients with no vomiting was higher in both HEC- and MEC-treated patients. This analysis demonstrates the consistent efficacy of aprepitant as part of an antiemetic regimen across different tumor types and chemotherapy regimens.

Fosaprepitant
In a randomized, parallel, double-blind, active-controlled study, fosaprepitant for injection 150 mg (N=1147) was compared with a 3-day oral aprepitant regimen (N=1175) (Table 1) in patients receiving a highly emetogenic chemotherapy regimen that included cisplatin (≥ 70 mg/m2). Patient demographics were similar between the two treatment groups.

Table 1: Treatment Regimens Highly Emetogenic Chemotherapy Trial*

	Day 1	Day 2	Day 3	Day 4
CINV Fosaprepitant Regimen				
Fosaprepitant	150 mg intravenously	none	none	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
Ondansetron	32 mg intravenously	none	none	none
CINV Aprepitant Regimen				
Aprepitant	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron	32 mg intravenously	none	none	none

*Fosaprepitant placebo, aprepitant placebo and dexamethasone placebo (in the evenings on days 3 and 4) were used to maintain blinding.
CINV: chemotherapy induced nausea and vomiting.

The efficacy of fosaprepitant 150 mg was evaluated based on the primary and secondary endpoints listed in Table 2 below and were shown to be non-inferior to that of the 3-day oral aprepitant regimen with regard to complete response in each of the evaluated phases. The pre-specified non-inferiority margin for complete response in the overall phase was 7%. The pre-specified non-inferiority margin for complete response in the delayed phase was 7.3%. The pre-specified non-inferiority margin for no vomiting in the overall phase was 8.2%.

Table 2: Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase

ENDPOINTS	Fosaprepitant Regimen (N = 1106)** %	Aprepitant Regimen (N = 1134)** %	Difference† (95% CI)
PRIMARY ENDPOINT			
Complete Response‡			
Overall§	71.9	72.3	-0.4 (-4.1, 3.3)
SECONDARY ENDPOINTS			
Complete Response‡			
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)

**N: Number of 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.

Mechanism 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 (NK1) 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).

Pharmacokinetic Properties
Absorption
Following a single, intravenous 150 mg dose of fosaprepitant administered as a 20 minute infusion to healthy volunteers, the mean AUC_{inf} of aprepitant was 37.38 (±14.75) mcg hr/mL and the mean maximal aprepitant concentration (C_{max}) was 4.15 (±1.15) mcg/mL.

Distribution
The mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 70 L in humans. It crosses the blood-brain barrier; plasma protein binding is reported to be more than 95%.

Metabolism
Aprepitant undergoes extensive hepatic metabolism, mainly via oxidation by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP1A2 and CYP2C19 mediate minor metabolic pathways. The resultant metabolites have weak activity.

Excretion
Aprepitant is not excreted unchanged in urine. The metabolites are excreted in the urine and via biliary excretion in the faeces. The terminal half-life is about 9 to 13 hours. The geometric mean plasma clearance of aprepitant following a 150 mg intravenous dose of fosaprepitant was approximately 73 mL/min.

Special Populations
Fosaprepitant pharmacokinetics has not been evaluated in special populations. No clinically relevant difference in aprepitant pharmacokinetics is expected due to age and gender.

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

Renal impairment:
A single 240 mg dose of oral aprepitant was administered to patients with severe renal impairment (CrCl< 30 mL/min) and to patients with end stage renal disease (ESRD) requiring haemodialysis. In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing haemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound aprepitant was not significantly affected in patients with renal impairment compared with healthy subjects. Haemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate. No dose adjustment is necessary for patients with renal impairment or for patients with ESRD undergoing haemodialysis.

Preclinical Safety Data
Preclinical data obtained with intravenous administration of fosaprepitant and oral administration of aprepitant reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity (including *in vitro* tests), and toxicity to reproduction. No clinically relevant carcinogenicity is demonstrated.

CLINICAL PARTICULARS
Therapeutic Indications
Fosaprepitant is given as part of a combination therapy with other antiemetic agents, indicated in adults for
- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Fosaprepitant has not been studied for the treatment of established nausea and vomiting. Chronic continuous administration is not recommended.

Posology and Method of Administration
Posology
Prevention of Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy (HEC)
Fosaprepitant dimeglumine for injection is administered intravenously on day 1 only as an infusion over 20 to 30 minutes initiated approximately 30 minutes prior to chemotherapy. Fosaprepitant should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in Table 3. Dexamethasone should be administered 30 minutes prior to chemotherapy 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 package insert for the co-administered 5-HT3 antagonist must be consulted prior to initiation of treatment

Table 3: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with Highly Emetogenic Cancer Chemotherapy

Drugs	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
HT3 antagonist	See the package insert for the selected 5-HT3 Antagonist.	none	none	none

Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy (MEC)
Fosaprepitant dimeglumine for injection is administered intravenously on day 1 only as an infusion over 20 to 30 minutes initiated approximately 30 minutes prior to chemotherapy. Fosaprepitant should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in Table 4. Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on day 1. The dose of dexamethasone accounts for active substance interactions. The package insert for the co-administered 5-HT3 antagonist must be consulted prior to initiation of treatment with fosaprepitant.

Table 4: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer Chemotherapy

Drugs	Day 1
Fosaprepitant	150 mg intravenously
Dexamethasone	12 mg orally
5-HT3 antagonist	See the package insert for the selected 5 HT3 antagonist.

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.

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Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. Fosaprepitant should be used with caution in these patients.

Paediatrics
The safety and efficacy of fosaprepitant in children and adolescents below 18 years of age has not yet been established.

Method of Administration
Fosaprepitant dimeglumine for injection should be administered intravenously and should not be given by the intramuscular or subcutaneous route. Intravenous administration occurs preferably through a running intravenous infusion over 20 to 30 minutes. Do not administer fosaprepitant as a bolus injection or undiluted solution.
For instructions on reconstitution and dilution of the fosaprepitant before administration (see **Special Precautions for Disposal and Other Handling** section).

Contraindications
- Hypersensitivity to the active substance or to polysorbate 80 or to any other excipients of the formulation.
- Co-administration of fosaprepitant with pimozide, terfenadine, astemizole or cisapride (see **Drug Interactions** section)

Special Warnings and Precautions for Use
Administration and Infusion Site Reactions
Fosaprepitant should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see **Posology and Method of Administration** section). Fosaprepitant should not be administered intramuscularly or subcutaneously. Mild injection site thrombosis has been reported at higher doses. If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

Co-administration with Substrates of CYP3A4 and CYP2C9
Concomitant administration of fosaprepitant with active substances that strongly induce or inhibit CYP3A4 activity (vinblastine, vincristine, or ifosfamide, cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, quinidine, irinotecan, ergot alkaloid derivatives, rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and protease inhibitors) should be avoided as the combination could result in reductions of the plasma concentrations of aprepitant.
Co-administration of oral aprepitant with a CYP2C9 substrates warfarin results in untoward effects. In patients on chronic warfarin therapy, the international normalized ratio (INR) should be monitored closely for 14 days following the use of fosaprepitant (see **Drug Interactions** section).

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
Isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnea have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. It is not recommended to re-initiate the infusion in patients who experience hypersensitivity reactions.

Hepatic Impairment
There is limited data in patients with moderate hepatic impairment and no clinical or pharmacokinetic data in patients with severe hepatic impairment. Therefore, caution should be exercised when fosaprepitant or aprepitant is administered in these patients.

Chronic Continuous Use
Chronic continuous use of fosaprepitant for injection for prevention of nausea and vomiting is not recommended because the drug interaction profile may change during chronic continuous use.

Drug Interactions
Aprepitant produces moderate inhibition of the cytochrome P450 isoenzyme CYP3A4. Therefore caution is required when using it with drugs that are primarily metabolized by this isoenzyme. Aprepitant should not be given with astemizole, cisapride, pimozide, or terfenadine as increased plasma concentrations of these drugs could cause serious life-threatening reactions. As aprepitant is also a substrate for CYP3A4, other drugs that inhibit or induce this isoenzyme may in turn increase or decrease plasma concentrations of aprepitant (see **Special Warnings and Precautions for Use** section). Aprepitant also causes a delayed induction of CYP2C9 and may lower plasma concentrations of drugs metabolized by this isoenzyme, such as warfarin, phenytoin, or tolbutamide. Caution is advised and additional monitoring may be appropriate in patients receiving other chemotherapeutic agents which are metabolized primarily or in part by CYP3A4 (e.g. etoposide, vinorelbine).
Aprepitant may also increase systemic exposure to corticosteroids; when given together it is recommended that the usual dose of oral dexamethasone be reduced by 50% and the dose of methylprednisolone by about 25% when given intravenously. The efficacy of oral contraceptives might be reduced by aprepitant (see **Special Warnings and Precautions for Use** section). It is recommended that alternative methods of contraception should be used during and for 1 to 2 months after stopping any dose of aprepitant.

Pregnancy and Lactation
There are no adequate and well-controlled studies in pregnant women. Therefore, this drug should be used during pregnancy only if clearly needed. It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants; a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on Ability to Drive and Use Machines
As aprepitant passes the blood brain barrier, it may have minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of fosaprepitant.

Undesirable Effects
Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant are expected to occur with fosaprepitant. The most common adverse effects associated with aprepitant are hiccups, increased alanine aminotransferase (ALT), dyspepsia, constipation, headache, decreased appetite and fatigue. Other reported effects with administration of aprepitant have included abdominal pain, oedema, tinnitus, flushing, epigastric discomfort, dysgeusia, dry mouth, stomatitis, thirst, polyuria, dysuria, haematuria, urinary frequency, arthralgia, myalgia, bradycardia, hyperglycaemia, disorientation, euphoria, anxiety, photosensitivity, and skin disorders. Anaemia and febrile neutropenia may also occur.

The safety profile of fosaprepitant was found almost similar to that seen with aprepitant. The following are adverse reactions reported in patients receiving fosaprepitant 150 mg when administered intravenously:
Vascular disorders: flushing, thrombophlebitis predominantly, infusion-site thrombophlebitis,
Skin and subcutaneous tissue disorders: erythema,
General disorders and administration site conditions: infusion site erythema, infusion site pain, infusion site pruritus, infusion site induration, immediate hypersensitivity reactions including flushing, erythema, dyspnoea,
Investigations: Increased blood pressure.

Overdose
There is no specific information on the treatment of overdosage 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. Due to antiemetic activity of aprepitant, drug-induced emesis may not be effective. Aprepitant cannot be removed by hemodialysis.

PHARMACEUTICAL PARTICULARS
Incompatibilities
This medicinal product must not be mixed with any other medicinal products except with those mentioned in (see **Special Precautions for Disposal and Other Handling** section).

Storage and Precautions
Storage: Store at a temperature between 2°C to 8°C.
Keep out of reach of children.

Shelf Life: Please refer carton/label.
After Reconstitution: The reconstituted solution when diluted with 0.9% sodium chloride Injection IP (150 mL) found to be stable at 25°C for 24 hours.

Special Precautions for Disposal and Other Handling
Instructions on Reconstitution and Dilution
1) Aseptically withdraw 5 mL of 0.9% Sodium Chloride for injection IP from 150 mL infusion bag. Aseptically inject 5 mL 0.9% Sodium Chloride for Injection IP (normal saline) into the vial. Assure that normal saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.
2) Aseptically prepare an infusion bag filled with 145 mL of normal saline.
3) Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing 145 mL of normal saline to yield a total volume of 150 mL and a final concentration of 1 mg/mL.
4) Gently invert the bag 2-3 times.
5) The reconstituted and diluted final drug solution should be inspected visually for particulate matter and discoloration before administration. For method of administration (see Posology and Method of Administration section).

The unused medicinal product should be disposed of according to the local requirements.

Nature and Contents of Container
FOSAPORT® is available as 150 mg single dose glass vial per carton.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

® - Registered trademark

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**.

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