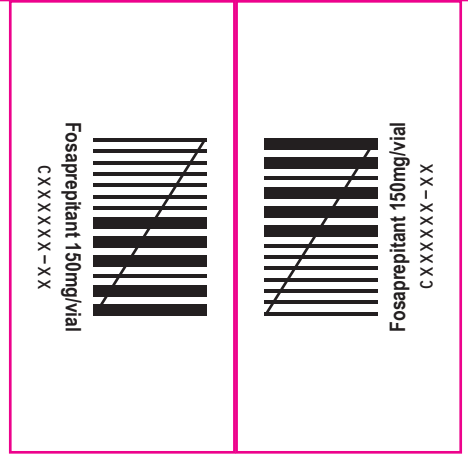

1. Name of the medicinal product

APRITANT IV POWDER FOR SOLUTION FOR INJECTION 150MG/VIAL (Fosaprepitant for Injection 150mg/vial)

2. Quality and Quantitative composition :

Each vial contains 245.3 mg fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant.

3. Pharmaceutical form

White to off white lyophilized cake or powder.

Description

Before reconstitution: White to off white lyophilized cake or powder in 10mL tubular(USP) Type-I clear vial with 13mm bromobutyl double slotted rubber stopper and sealed with aluminium seal having polypropylene disc.

After reconstitution: Clear, colorless to pale yellow solution free from visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fosaprepitant for injection is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:

- highly emetogenic cancer chemotherapy
- moderately emetogenic cancer chemotherapy.

Fosaprepitant for injection should be given in combination with a corticosteroid and a 5-HT_3 antagonist.

4.2 Posology and method of administration

Apritant IV for intravenous administration is a lyophilized prodrug of aprepitant containing polysorbate 80 (PS80).

Apritant IV is administered on Day 1 as an infusion over 20 – 30 minutes initiated approximately 30 minutes prior to chemotherapy. Apritant IV, should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in the tables below. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with Apritant IV.

Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

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

	Day 1	Day 2	Day 3	Day 4
APRITANT IV	150 mg IV	none	none	none
Dexamethasone*	12 mg orally	8 mg orally	8 mg orally bid	8 mg orally bid
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for the 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 through 4. Dexamethasone should also be administered in the evenings on Days 3 and 4. The dose of dexamethasone accounts for drug interactions.

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

	Day 1
APRITANT IV	150 mg IV
Dexamethasone*	12 mg orally
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for the appropriate dosing information.

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

Method of administration

APRITANT IV powder for solution for injection 150mg/vial should be administered intravenously.

Preparation of Apritant IV for Injection 150 mg

1. Aseptically inject 5 ml 0.9% saline into the vial. Assure that 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 saline.
3. Aseptically withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 ml of saline to yield a total volume of 150 ml. Gently invert the bag 2-3 times.

The reconstituted solution should be used immediately; although 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.

Apritant IV is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Hartman's and Lactated Ringer's Solution. Apritant IV must not be reconstituted or mixed with solutions for which physical and chemical compatibility have not been established.

GENRAL INFORMATION

See Interaction with other medicinal products and other forms of interaction for additional information on the administration of Apritant IV with corticosteroids.

Refer to the full prescribing information for coadministered antiemetic agents.

No dosage adjustment is necessary based on age, gender, race or Body Mass Index (BMI).

No dosage adjustment is necessary for patients with severe renal insufficiency (creatinine clearance <30ml/min) or for patients with end stage renal disease undergoing hemodialysis.

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9)

4.3 Contraindications

Apritant IV is contraindicated in patients who are hypersensitive to APRITANT IV powder for solution for injection 150mg/vial, aprepitant, polysorbate 80 or any other components of the product.

Apritant IV should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Since fosaprepitant is rapidly converted to aprepitant (a weak to moderate inhibitor of CYP3A4), fosaprepitant should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolized through CYP3A4; some chemotherapy agents are metabolized by CYP3A4 (see Interaction with other medicinal products and other forms of interaction). Weak inhibition of CYP3A4 by fosaprepitant 150 mg could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see Interaction with other medicinal products and other forms of interaction). Consequently, chemotherapeutic agents metabolized via CYP3A4 should be used with caution. Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination may result in increased toxicity.

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. 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.

There are limited data in patients with moderate hepatic insufficiency and no data in patients with severe hepatic insufficiency. Fosaprepitant should be used with caution in these patients.

Coadministration of fosaprepitant with ergot alkaloid derivatives, which are CYP3A4 substrates, may result in elevated plasma concentrations of these medicinal products. Therefore, caution is advised due to the potential risk of ergot-related toxicity.

Concomitant administration of fosaprepitant with medicinal products that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant.

Concomitant administration of aprepitant with St. John's wort is not recommended.

Concomitant administration of fosaprepitant with medicinal products that inhibit CYP3A4 activity (e.g., ritonavir, ketoconazole, clarithromycin, telithromycin) should be approached cautiously as the combination results in increased plasma concentrations of aprepitant.

Immediate hypersensitivity reactions including flushing, erythema, dyspnea, 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.

Infusion site reactions (ISRs) have been reported with the use of Apritant IV (see Undesirable effects). 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.

Coadministration of fosaprepitant 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 (see Interaction with other medicinal products and other forms of interaction).

The efficacy of hormonal contraceptives during and for 28 days after administration of fosaprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 1 month following administration of fosaprepitant (see Interaction with other medicinal products and other forms of interaction).

Chronic continuous use of Apritant IV 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. Apritant IV 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). Apritant IV should not be administered intramuscularly or subcutaneously. Mild injection site thrombosis has been observed at higher doses (see Overdose). If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

4.5 Interaction with other medicinal products and other forms of interaction

When administered intravenously, fosaprepitant is rapidly converted to aprepitant. Therefore, drug interactions following administration of fosaprepitant are likely to occur with drugs that interact with oral aprepitant. The following information was derived from studies conducted with oral aprepitant and studies conducted with fosaprepitant coadministered with dexamethasone, midazolam or diltiazem.

Aprepitant is a substrate, a weak to moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

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 metabolized through CYP3A4. The total exposure of CYP3A4 substrates may increase up to 2-fold on Days 1 and 2 after coadministration with a single 150 mg fosaprepitant dose. Fosaprepitant must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by fosaprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. (See Contraindications). Caution is advised during concomitant administration of fosaprepitant and active substances that are metabolized primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see Special warnings and precautions for use).

Effect of fosaprepitant/aprepitant on the pharmacokinetics of other agents

Aprepitant, as a weak to moderate inhibitor of CYP3A4, and fosaprepitant, as a weak inhibitor of CYP3A4, can increase plasma concentrations of orally coadministered medicinal products that are metabolized through CYP3A4.

Fosaprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see Contraindications).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of fosaprepitant with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

Fosaprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical drug interaction study.

5-HT_3 antagonists: In clinical drug interaction studies, aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg on Days 2 and 3, did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids: Dexamethasone: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the AUC0-24hr of dexamethasone, a CYP3A4 substrate, by approximately 2.0-fold on Days 1 and 2 when dexamethasone was coadministered as a single 8 mg oral dose on Days 1, 2, and 3. The oral dexamethasone dose on Days 1 and 2 should be reduced by approximately 50% when coadministered with fosaprepitant 150 mg IV on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without fosaprepitant 150 mg (see Posology and method of administration).

Methylprednisolone: Oral aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.3-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

Chemotherapeutic agents: In clinical studies, the oral aprepitant regimen was administered with the following chemotherapeutic agents metabolized primarily or in part by CYP3A4: etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. Caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4. Post marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see Special warnings and precautions for use).

Docetaxel: In a separate pharmacokinetic study, oral aprepitant, (CINV regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a separate pharmacokinetic study, oral aprepitant (CINV regimen) did not influence the pharmacokinetics of vinorelbine.

Warfarin: A single 125 mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) through concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

Tolbutamide: Oral aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15.

Oral contraceptives: Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%.

In another study, a single dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21 with oral aprepitant, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there was as much as a 64% decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of oral aprepitant on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21.

The efficacy of hormonal contraceptives during and for 28 days after administration of fosaprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with fosaprepitant and for 1 month following administration of fosaprepitant.

Midazolam: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the AUC0-∞ of midazolam by approximately 1.8-fold on Day 1 and had no effect (1.0-fold) on Day 4 when midazolam was coadministered as a single oral dose of 2 mg on Days 1 and 4. Fosaprepitant 150 mg I.V 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.

Effect of other agents on the pharmacokinetics of aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of fosaprepitant with strong CYP3A4 inhibitors (e.g.,ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached cautiously. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in a 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations and decreased efficacy.

Ketoconazole: When a single 125 mg dose of oral aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of fosaprepitant with strong CYP3A4 inhibitors should be approached cautiously.

Rifampin: When a single 375 mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold. Coadministration of fosaprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy.

Additional interactions

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 1.5-fold increase of aprepitant AUC and a 1.4 fold increase in diltiazem AUC. The pharmacokinetic effects resulted in a small but clinically meaningful decrease in diastolic blood pressure (decrease of 16.8 mm Hg with fosaprepitant versus 10.5 mm Hg without fosaprepitant) and may result in a small but clinically meaningful decrease in systolic blood pressure (decrease of 24.4 mm Hg with fosaprepitant versus 18.8 mm Hg without fosaprepitant), but did not result in a clinically meaningful change in heart rate, or PR interval, beyond those changes induced by diltiazem alone.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and Cmax by approximately 20% of both aprepitant and paroxetine.

4.6 Fertility, Pregnancy and Lactation and Other Special Populations

Pregnancy:

Apritant IV should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the foetus.

Risk Summary

There are insufficient data on use of fosaprepitant in pregnant women to inform a drug associated risk. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug levels (AUC) approximately equivalent to the exposure at the recommended human dose (RHD) of 150 mg.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1,000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 25 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1,000 mg/kg twice daily and in pregnant rabbits at 25 mg/kg/day were approximately equivalent to the exposure at the RHD of 150 mg. Aprepitant crosses the placenta in rats and rabbits.

Lactation

Apritant IV when administered intravenously, is rapidly converted to aprepitant.

Risk Summary

Lactation studies have not been conducted to assess the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for fosaprepitant and any potential adverse effects on the breastfed infant from fosaprepitant or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

Upon administration of fosaprepitant, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use an effective alternative or back-up non-hormonal contraceptive (such as condoms and spermicides) during treatment with fosaprepitant and for 1 month following the last dose.

Paediatric Use:

APRITANT IV has not been approved for use in paediatric patients.

Elderly Use :

In clinical studies, the efficacy and safety of aprepitant in the elderly (≥ 65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is necessary in elderly patients.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Since fosaprepitant is converted to aprepitant, those adverse experiences associated with aprepitant might also be expected to occur with APRITANT IV powder for solution for injection 150mg/vial.

The overall safety of fosaprepitant was evaluated in approximately 1600 individuals, and the overall safety of aprepitant was evaluated in approximately 6800 individuals.

Oral Aprepitant

Highly Emetogenic Chemotherapy (HEC)

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 544 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. The 3-day oral aprepitant regimen was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, drug-related clinical adverse experiences were reported in approximately 19% of patients treated with the 3-day oral aprepitant regimen compared with approximately 14% of patients treated with standard therapy. Treatment was discontinued due to drug-related clinical adverse experiences in 0.6% of patients treated with the 3-day oral aprepitant regimen compared with 0.4% of patients treated with standard therapy.

The most common drug-related adverse experiences reported in patients treated with the 3-day oral aprepitant regimen and greater than standard therapy were: hiccups (4.6%), ALT increased (2.8%), dyspepsia (2.6%), constipation (2.4%), headache (2.0%), and decreased appetite (2.0%).In an additional active-controlled clinical study in 1169 patients receiving the 3-day oral aprepitant regimen and HEC, the adverse experience profile was generally similar to that seen in the other HEC studies with the 3-day oral aprepitant regimen.

Moderately Emetogenic Chemotherapy (MEC)

In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), 868 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, the 3-day oral aprepitant regimen was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In the combined analysis of Cycle 1 data for these 2 studies, drug-related adverse experiences were reported in approximately 14% of patients treated with the 3-day oral aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to drug-related adverse experiences in 0.7% of patients treated with the 3-day oral aprepitant regimen compared with 0.2% of patients treated with standard therapy.

The most common drug-related adverse experience reported at a greater incidence in patients treated with the 3-day oral aprepitant regimen than with standard therapy was fatigue (1.4%).

Highly and Moderately Emetogenic Chemotherapy

In a pooled analysis of the HEC and MEC studies, the following drug-related adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen and at a greater incidence than standard therapy:

[Common (≥ 1/100, <1/10), Uncommon (≥ 1/1,000, <1/100), Rare (≥ 1/10,000, <1/1,000)]

Infection and infestations:

Rare: candidiasis, staphylococcal infection.

Blood and the lymphatic system disorders:

Uncommon: anemia, febrile neutropenia.

Metabolism and nutrition disorders:

Common: decreased appetite

Rare: polydipsia.

Psychiatric disorders:

Uncommon: anxiety

Rare: disorientation, euphoric mood.

Nervous system disorders:

Uncommon: dizziness, somnolence

Rare: cognitive disorder, lethargy, dysgeusia.

Eye disorders:

Rare: conjunctivitis.

Ear and labyrinth disorders:
Rare: tinnitus.

Cardiac disorders:
Uncommon: palpitations
Rare: bradycardia, cardiovascular disorder.

Vascular disorders:
Uncommon: hot flush.

Respiratory, thoracic and mediastinal disorders:
Common: hiccups
Rare: oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation

Gastrointestinal disorders:
Common: dyspepsia
Uncommon: eructation, nausea, gastroesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence
Rare: feces hard, duodenal ulcer perforation, neutropenic colitis, stomatitis, abdominal distension.

Skin and subcutaneous tissue disorders:
Uncommon: rash, acne
Rare: photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic.

Musculoskeletal and connective tissue disorders:
Rare: muscle spasms, muscular weakness.

Renal and urinary disorders:
Uncommon: dysuria
Rare: pollakiuria.

General disorders and administration site conditions:
Common: fatigue
Uncommon: asthenia, malaise
Rare: edema, chest discomfort, gait disturbance.

Investigations:
Common: ALT increased
Uncommon: AST increased, blood alkaline phosphatase increased
Rare: urine output increased, red blood cells urine positive, blood sodium decreased, weight decreased, glucose urine present, neutrophil count decreased.
The adverse experience profiles in the Multiple-Cycle extensions of HEC and MEC studies for up to 6 cycles of chemotherapy were generally similar to those observed in Cycle 1.
In another CINV study, Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy.

Fosaprepitant

Moderately Emetogenic Chemotherapy (MEC)
In an active-controlled clinical trial in patients receiving MEC, safety was evaluated in 504 patients receiving a single dose of fosaprepitant IV in combination with ondansetron and dexamethasone (fosaprepitant regimen) compared to 497 patients receiving ondansetron and dexamethasone alone (control regimen). The following clinically important drug-related adverse experiences were reported in patients treated with the fosaprepitant regimen and at a greater incidence than in the control group.
[Common (≥ 1/100, <1/10) Uncommon (≥ 1/1000, <1/100)]

Cardiac disorders:
Uncommon: palpitations.

Gastrointestinal disorders:
Common: constipation
Uncommon: abdominal distension, abdominal pain, abdominal pain upper, dyspepsia.

General disorders and administration site conditions:
Common: infusion site pain
Uncommon: asthenia.

Infections and infestations:
Uncommon: oral candidiasis.

Metabolism and nutrition disorders:
Uncommon: decreased appetite.

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough, oropharyngeal pain, throat irritation.

Vascular disorders:
Uncommon: hot flush.

Highly Emetogenic Chemotherapy (HEC)
In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1143 patients receiving a single dose of fosaprepitant IV 150mg compared to 1169 patients receiving the 3-day regimen of aprepitant. The safety profile was generally similar to that seen in the MEC study with fosaprepitant.

The following additional clinically important drug-related adverse experiences occurred with fosaprepitant 150 mg and have not been reported in earlier clinical studies with oral aprepitant, or in the MEC study with fosaprepitant.

[Uncommon (≥ 1/1,000, <1/100), Rare (≥ 1/10,000, <1/1,000)]

General disorders and administration site conditions:
Uncommon: infusion site erythema, infusion site pruritus
Rare: infusion site induration.

Investigations:
Uncommon: blood pressure increased.

Skin and subcutaneous tissue disorders:
Uncommon: erythema.

Vascular disorders:

Uncommon: flushing, thrombophlebitis (predominantly, infusion-site thrombophlebitis).

Other Studies

Single 40 mg doses of aprepitant have also been studied for the prevention of post-operative nausea and vomiting (PONV) in non-chemotherapy patients receiving general balanced anesthesia. In these studies, additional adverse reactions that were observed at a greater incidence than with the active comparator (ondansetron) included: ALT increased, abdominal pain upper, bowel sounds abnormal, dysarthria, dyspnea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, visual acuity reduced, wheezing.

In addition, two serious adverse experiences were reported in PONV clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of sub-ileus.

One case of angioedema and urticaria was reported as a serious adverse event in a patient receiving aprepitant in a non-CINV/non-PONV study.

Post-Marketing Experience:
The following adverse reactions have been identified during post-marketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the drug.

Skin and subcutaneous tissue disorders:
pruritus, rash, urticaria, rarely Stevens-Johnson
syndrome/toxic epidermal necrolysis

Immune system disorders:
hypersensitivity reactions including anaphylactic reactions/anaphylactic shock
Immediate hypersensitivity reactions have been observed during the infusion of fosaprepitant which may include the following: flushing, erythema, dyspnea (see Special warnings and precautions for use).

4.9 Overdose
No specific information is available on the treatment of overdosage. Single doses up to 200 mg of fosaprepitant IV and 600 mg of aprepitant were generally well tolerated in healthy subjects. Three out of 33 subjects receiving 200 mg of fosaprepitant experienced mild injection site thrombosis. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375 mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated.

Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

In the event of overdose, APRITANT IV powder for solution for injection 150mg/vial 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK1) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/ml) within 30 minutes of the completion of infusion.

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 at human substance P neurokinin 1 (NK1) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing CINV therapy.

NK1-receptor antagonists have been shown pre-clinically to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Preclinical and human Positron Emission Tomography (PET) studies with aprepitant have shown that it is brain penetrant and occupies brain NK1 receptors. Preclinical studies show that aprepitant has a long duration of central activity, inhibits both the acute and delayed phases of cisplatin-induced emesis, and augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

5.2 Pharmacokinetic properties
Absorption
Following a single intravenous 150 mg dose of fosaprepitant administered as a 20-minute infusion to healthy volunteers the mean $AUC_{0-\infty}$ of aprepitant was 35.0 mcg· hr/ml and the mean maximal aprepitant concentration was 4.01 mcg/ml.

Distribution
Fosaprepitant is rapidly converted to aprepitant.
Aprepitant is greater than 95% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 66 L in humans.
Aprepitant crosses the placenta in rats, and crosses the blood brain barrier in rats and ferrets. *PET studies in humans indicate that aprepitant crosses the blood brain barrier (see Pharmacodynamic Properties, Mechanism of action).*

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 healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [^{14}C]-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. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. In vitro studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.
All metabolites observed in urine, feces 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 free acid) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

Elimination
Following administration of a single IV 100 mg dose of [^{14}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. Following administration of a single oral 300 mg dose of [^{14}C]-aprepitant to healthy subjects, 5% of the radioactivity was recovered in urine and 86% in feces.
The apparent terminal half-life of aprepitant ranged from approximately 9 to 13 hours.

Characteristics in Patients
Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant.

Gender
Following oral administration of a single dose of aprepitant, the $AUC_{0\text{-}24hr}$ and C_{max} for aprepitant are 9% and 17% higher, respectively, in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and its T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Elderly
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 $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥ 65 years) relative to younger adults. The C_{max} 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.

Paediatric
Fosaprepitant has not been approved for use in paediatric patients.

Race
Following oral administration of a single dose of aprepitant, the $AUC_{0\text{-}24hr}$ is approximately 27% and 31% higher in Hispanics as compared with Caucasians and Blacks, respectively. The C_{max} is 19% and 29% higher in Hispanics as compared with Caucasians and Blacks, respectively. Single dose administration of oral aprepitant in Asians resulted in a 74% and 47% increase in $AUC_{0\text{-}24hr}$ and C_{max}, respectively, as compared to Caucasians. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on race.

Body Mass Index (BMI)
Body Mass Index (BMI) had no clinically meaningful effect on the pharmacokinetics of aprepitant.

Hepatic Insufficiency
Fosaprepitant is metabolized in various extrahepatic tissues; therefore, hepatic insufficiency is not expected to alter the conversion of fosaprepitant to aprepitant.
Oral aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. 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 insufficiency (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 insufficiency (ChildPugh score 7 to 9), the $AUC_{0\text{-}24hr}$ 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 insufficiency.
There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).

Renal Insufficiency
A single 240 mg dose of oral aprepitant was administered to patients with severe renal insufficiency (CrCl<30 ml/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.
In patients with severe renal insufficiency, the $AUC_{0\text{-}\infty}$ 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 hemodialysis, the $AUC_{0\text{-}\infty}$ 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 drug was not significantly affected in patients with renal insufficiency 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 severe renal insufficiency or for patients with ESRD undergoing hemodialysis.

Pharmacodynamics
Cardiac Electrophysiology
In a randomized, double-blind, positive controlled, thorough QTc study, a single 200 mg dose of fosaprepitant had no clinically significant effect on the QTc interval.

Brain NK1 Receptor Occupancy Assessed by Positron Emission Tomography
A positron emission tomography study 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 Preclinical safety data

Carcinogenesis
Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1,000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to (female rats) or less than (male rats) the adult human exposure at the RHD of 150 mg. Treatment with aprepitant at doses of 5 to 1,000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1,000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2,000 mg/kg/day. The highest dose produced a systemic exposure approximately 2 times the adult human exposure at the RHD of 150 mg. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Mutagenesis
Aprepitant and fosaprepitant were not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Impairment of Fertility
Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant. In the fertility studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. Oral aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1,000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended adult human dose of 150 mg and exposure in female rats approximately equivalent to the adult human exposure).

Information for Patients:
Physicians should instruct their patients to read the patient package insert before starting therapy with APRITANT IV and to reread it each time the prescription is renewed.

Patients should follow the physician's instructions for the APRITANT IV regimen. For the prevention of CINV, patients can be given a single dose of APRITANT IV as an infusion over 20– 30 minutes, 30 minutes prior to chemotherapy on Day 1.

Advise patients to seek medical attention if they experience new or worsening signs or symptoms of an infusion site reaction, such as erythema, edema, pain, necrosis, vasculitis, or thrombophlebitis at or near the infusion site (see Special warnings and precautions for use).

APRITANT IV may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

Concomitant administration of APRITANT IV may reduce the efficacy of hormonal contraceptives. Patients should be advised to use alternative or back-up methods of contraception during treatment with and for 1 month following administration of APRITANT IV.

6.0 Pharmaceutical particulars

6.1 List of excipients:
Disodium edetate, Polysorbate 80, Lactose anhydrous, Sodium hydroxide (for pH adjustment) and Hydrochloric acid diluted (for pH adjustment).

6.2 Incompatibilities :
APRITANT IV is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Hartman's and lactated Ringer's solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in Special precautions for disposal and other handling.

6.3 Special precautions for storage:
Store in a refrigerator (2°C – 8°C).
After reconstitution in primary container with 0.9 % Sodium chloride injection and further infusion with 0.9% sodium chloride Injection USP, based on physical and chemical stability evaluation,the reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

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

6.4 Nature and contents of container :
10 mL tubular (USP) Type I clear glass vial with a 13 mm bromobutyl double slotted rubber stopper and sealed with aluminium seal having polypropylene disc
Pack sizes: 1 vial.

6.5 Special precautions for disposal and other handling:
Fosaprepitant 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)].

APRITANT IV must be reconstituted and then diluted prior to administration.

Preparation of APRITANT IV powder for solution for injection 150mg/vial for intravenous administration:

1. Aseptically inject 5 ml 0.9% saline into the vial. Assure that 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 saline.
3. Aseptically withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 ml of saline to yield a total volume of 150 ml. Gently invert the bag 2-3 times.

The reconstituted solution should be used immediately; although 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.

APRITANT IV powder for solution for injection 150mg/vial is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Hartman's and Lactated Ringer's Solution. APRITANT IV powder for solution for injection 150mg/vial must not be reconstituted or mixed with solutions for which physical and chemical compatibility have not been established.

7. Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
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8. Product Registrant:
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9. Date of Revision of Text
April 2024.

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