PRODUCT INFORMATION
FOSAPREPITANT-AFT (FOSAPREPITANT DIMEGLUMINE) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

Fosaprepitant dimeglumine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Fosaprepitant-AFT 150 mg for intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant free acid.

Excipients with known effect:

Anhydrous lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Fosaprepitant-AFT is a white to off-white lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fosaprepitant-AFT, in combination with a corticosteroid and a 5-HT3 antagonist, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:

- highly emetogenic cancer chemotherapy (see Section 4.2 Dose and Method of Administration)
- moderately emetogenic cancer chemotherapy (see Section 4.2 Dose and Method of Administration).

4.2 Dose and method of administration

Dose

Fosaprepitant-AFT, for administration by intravenous infusion, is a lyophilised prodrug of aprepitant containing polysorbate 80.

Fosaprepitant-AFT 150 mg is administered on day 1 as an infusion over 20-30 minutes initiated approximately 30 minutes prior to chemotherapy. Fosaprepitant-AFT should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in Tables 1 and Table 2. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with Fosaprepitant-AFT 150 mg.

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

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

Special populations

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

Renal impairment

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

Hepatic impairment

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).

Method of administration

1. Inject 5 mL 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.*

4. To avoid microbiological hazard, Fosaprepitant-AFT solution should be used as soon as practicable after reconstitution and further dilution. If storage is unavoidable, the solution should be held below 25°C for not more than 24 hours.

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

6. Fosaprepitant-AFT 150 mg should only be administered as an infusion over **20-30 minutes.**

Fosaprepitant-AFT is for single use in one patient only. Discard any residue.

* Please Note: there is a 5% overfill in each vial to account for non-withdrawable losses and to ensure that the labelled dose of 150 mg is deliverable after reconstitution.

General information

See Section 4.5 Interactions with Other Medicines and Other Forms of Interactions for additional information on the administration of Fosaprepitant-AFT with corticosteroids.

Refer to the full prescribing information for coadministered antiemetic agents.

4.3 Contraindications

Fosaprepitant-AFT is contraindicated in patients who are hypersensitive to Fosaprepitant-AFT, aprepitant, polysorbate 80 or any other components of the product.

Fosaprepitant-AFT 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). Weak inhibition of CYP3A4 by fosaprepitant 150 mg could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). 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 fosaprepitant (see section 4.8 Adverse 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 Section 4.5 Interaction with other medicines 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 Section 4.5 Interaction with other medicines and other forms of interaction).

Chronic continuous use of Fosaprepitant-AFT 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.

Fosaprepitant-AFT should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see section 4.2 Dose and method of administration). Fosaprepitant-AFT should not be administered intramuscularly or subcutaneously. Mild injection site thrombosis has been observed at higher doses. If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

Use in the elderly

See Section 5.2 Pharmacokinetic Properties, Elderly.

Paediatric use

See Section 5.2 Pharmacokinetic Properties, Paediatric patients.

Effects on laboratory tests

See Section 4.4 Special Warnings and Precautions for Use, INR monitoring as mentioned above, and Section 4.5 Interactions with other medicines and other forms of interactions, Warfarin.

4.5 Interaction with other medicines 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 section 4.3 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 section 4.4 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 section 4.3 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 $AUC_{0\text{-}24}$ hr 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 Section 4.2 Dose 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 Section 4.4 Special Warnings and Precautions for Use).

Docetaxel: In an interaction 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) trough 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 µg of ethinylestradiol and 1 mg of norethindrone, decreased the AUC of ethinylestradiol by 43%, and decreased the AUC of norethindrone by 8%.

In another study, a single dose of an oral contraceptive containing ethinylestradiol 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 ethinylestradiol decreased by 19% on day 10 and there was as much as a 64% decrease in ethinylestradiol 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 IV 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 (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.

Rifampicin

When a single 375-mg dose of oral aprepitant was administered on day 9 of a 14-day regimen of 600 mg/day of rifampicin, 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 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 C_{max} by approximately 20% of both aprepitant and paroxetine.

4.6 Pregnancy and lactation

Use in pregnancy

There are no adequate and well-controlled studies in pregnant women. Fosaprepitant-AFT should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus.

Use in nursing mothers

Fosaprepitant-AFT, when administered intravenously, is rapidly converted to aprepitant.

Aprepitant is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of aprepitant on 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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, certain side effects that have been reported with Fosaprepitant-AFT may affect some patients' ability to drive or operate machinery. Individual responses to Fosaprepitant-AFT may vary.

4.8 Adverse effects (Undesirable effects)

The overall safety of fosaprepitant was evaluated in approximately 1600 individuals.

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 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 highly emetogenic chemotherapy, safety was evaluated for 1143 patients receiving a single dose of fosaprepitant 150 mg 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 (≥1/1000, <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)

Since fosaprepitant is converted to aprepitant, those adverse experiences associated with aprepitant might also be expected to occur with fosaprepitant. See the package insert for oral aprepitant products for complete safety information regarding studies performed with oral aprepitant.

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 or anaphylactic reactions have been observed during the infusion of fosaprepitant which may include the following: flushing, erythema, rash, chest tightness, wheezing, dyspnoea (see Section 4.4 Special Warnings and Precaution for Use).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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.

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, Fosaprepitant-AFT 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 haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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

Aprepitant has a unique mode of action; it is a selective high affinity antagonist at human substance P neurokinin 1 (NK_1) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK_1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are the targets of existing therapy for chemotherapy-induced nausea and vomiting (CINV).

NK_1-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 NK_1 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.

Cardiac electrophysiology

In a randomised, double-blind, positive controlled, thorough QTc study, a single 200 mg dose of fosaprepitant had no effect on the QTc interval.

Brain NK_1 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 NK_1 receptor occupancy of ≥100% at T_{max}, and 24 hours, ≥97% at 48 hours, and between 41% and 75% at 120 hours, following dosing. Occupancy of brain NK_1 receptors, in this study, correlate well with aprepitant plasma concentrations.

5.2 Pharmacokinetic properties

Absorption

Fosaprepitant-AFT is dosed intravenously and therefore is immediately and completely bioavailable.

Aprepitant after Fosaprepitant Administration

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 µg.hr/mL and the mean maximal aprepitant concentration was 4.01 µg/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 Section 5.1 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 metabolised primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.

All metabolites observed in urine, faeces and plasma following an intravenous 100 mg [^{14}C]-fosaprepitant dose were also observed following an oral dose of [^{14}C]-aprepitant. Upon conversion of 245.3 mg of fosaprepitant dimeglumine (equivalent to 150 mg fosaprepitant free acid) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

Excretion

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 faeces.

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 faeces.

The apparent terminal half-life of aprepitant ranged from approximately 9 to 13 hours .

Special populations

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.

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.

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 haemodialysis.

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 haemodialysis, the $AUC_{0-\infty}$ 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 drug was not significantly affected in patients with renal insufficiency 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 dosage adjustment for Fosaprepitant-AFT is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing haemodialysis, based on the pharmacokinetics of aprepitant in these patients, although no clinical studies have been conducted to determine whether efficacy is affected.

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_{0-24hr} 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 (Child-Pugh score 7 to 9), the AUC_{0-24hr} 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_{0-24hr} 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).

Paediatric patients

Fosaprepitant has not been evaluated in patients below 18 years of age.

5.3 Preclinical safety data

Genotoxicity

Fosaprepitant and aprepitant were both negative in the following genotoxicity assays: in vitro microbial and TK6 human lymphoblastoid cell mutagenesis assays, the in vitro alkaline elution/rat hepatocyte DNA strand break test, the in vitro chromosomal aberration assay in Chinese hamster ovary cells, and the in vivo mouse micronucleus assay in bone marrow.

Carcinogenicity

Carcinogenicity studies were not conducted with fosaprepitant but studies were conducted with aprepitant in mice and rats for approximately 2 years. In mice, aprepitant was not carcinogenic at doses

up to 500 mg/kg/day (approximately 2 times the adult human dose based on systemic exposure). Rats developed hepatocellular adenomas at a dose of 25 mg/kg twice daily (females) and 125 mg/kg twice daily (males), thyroid follicular cell adenomas at a dose of 125 mg/kg twice daily (females and males), and thyroid follicular cell carcinomas at a dose of 125 mg/kg twice daily (males). Systemic exposures at these doses in rats were approximately equivalent to or lower than exposures in humans at the recommended dose. Tumours of these types are considered to be a consequence of hepatic CYP enzyme induction in the rat, and are consistent with changes observed in rats with other structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic CYP enzymes. Consideration of the mechanisms involved in the development of these tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of fosaprepitant or aprepitant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each vial of Fosaprepitant-AFT 150 mg contains the following inactive ingredients: disodium edetate, polysorbate 80, anhydrous lactose, sodium hydroxide and/or hydrochloric acid (for pH adjustment).

6.2 Incompatibilities

Fosaprepitant-AFT is incompatible with any solutions containing divalent cations (e.g., Ca2+, Mg2+), including Hartman’s and Lactated Ringer’s Solution. Fosaprepitant-AFT must not be reconstituted or mixed with solutions for which physical and chemical compatibility have not been established.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store at 2 to 8°C (Refrigerate. Do not freeze).

6.5 Nature and contents of container

Fosaprepitant-AFT 150 mg is available as a single dose vial containing 150 mg of Fosaprepitant, in cartons containing 1 vial.

6.6 Special precautions for disposal

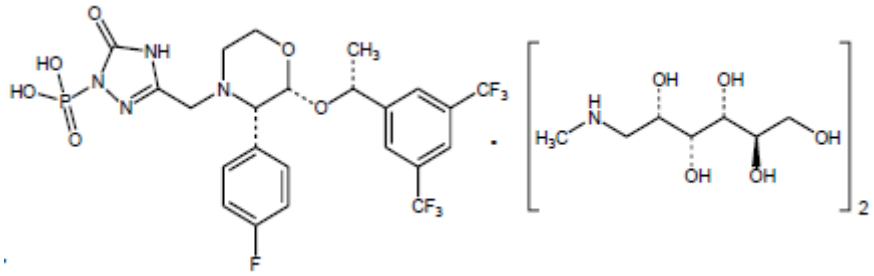
Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Fosaprepitant dimeglumine is a white to off-white amorphous powder. It is freely soluble in water. Fosaprepitant dimeglumine is a prodrug of aprepitant and is chemically described as 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).

Its empirical formula is C23H22F7N4O6P, 2(C7H17NO5) with a molecular weight of 1004.83.

Chemical structure



CAS number

265121-04-8.

7. FORENSIC CLASSIFICATION

Prescription Only Medicine

8. PRODUCT OWNER

AFT Pharmaceuticals Ltd
Auckland
New Zealand

9. DATE OF FIRST APPROVAL

[Date of Approval]

10. DATE OF REVISION

[Date of Approval]