INAPITANT

1. NAME OF THE MEDICINAL PRODUCT

INAPITANT TRI-PACK CAPSULE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 80mg or 125mg of aprepitant. For excipients, see 7.1.

3. PHARMACEUTICAL FORM

Hard capsule.
80mg Capsule: Opaque hard gelatin No 2 capsules with a white cap and white body, printed with "80mg" on the body.

125mg Capsule: Opaque hard gelatin No 1 capsules with a pink cap and white body, printed with "125mg" on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INAPITANT 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

INAPITANT should be given in combination with a corticosteroid and a 5-HT_3 antagonist.

4.2 Posology and method of administration

INAPITANT is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose of INAPITANT is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with INAPITANT.

INAPITANT has not been studied for the treatment of established nausea and vomiting.

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

	Day 1	Day 2	Day 3	Day 4
INAPITANT	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally

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. The dose of dexamethasone was chosen to account for drug interactions.

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

	Day 1	Day 2	Day 3
INAPITANT	125 mg orally	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.	none	none

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

Chronic continuous administration is not recommended.

See 4.5 for additional information on the administration of INAPITANT with corticosteroids.

Refer to the full prescribing information for co-administered antiemetic agents.

INAPITANT may be taken with or without food.

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 <30 mL/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

Aprepitant is contraindicated in patients who are hypersensitive to any component of the product.

Aprepitant 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 4.5).

4.4 Special warnings and precautions for use

Aprepitant 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. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products administered orally. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates. 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. Aprepitant should be used with caution in these patients.

Co-administration of aprepitant 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 aprepitant with medicinal products that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazapine, 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 aprepitant 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.

Chronic continuous use of aprepitant 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.

Co-administration of aprepitant with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of aprepitant with each chemotherapy cycle.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of aprepitant on the pharmacokinetics of other agents

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally co-administered medicinal products that are metabolized through CYP3A4. Aprepitant can increase plasma concentrations of intravenously co-administered medicinal products metabolized through CYP3A4 to a lesser extent.

Aprepitant 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.

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Co-administration of aprepitant 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.

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

5-HT$_3$ antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids:

Dexamethasone: Aprepitant, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and aprepitant when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate by 2.2-fold, on Days 1 and 5. The usual oral dexamethasone doses should be reduced by approximately 50% when co-administered with aprepitant, to achieve exposures of dexamethasone similar to those obtained when it is given without aprepitant. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting studies with aprepitant reflects an approximate 50% reduction of the dose of dexamethasone (see 4.2).

Methylprednisolone: 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 co-administered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The usual IV methylprednisolone dose should be reduced by approximately 25%, and the usual oral methylprednisolone dose should be reduced by approximately 50% when co-administered with aprepitant, to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant.

Chemotherapeutic agents: In clinical studies, aprepitant 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. Postmarketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosamide co-administration.

Docetaxel: In a separate pharmacokinetic study, aprepitant did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a separate pharmacokinetic study, aprepitant did not influence the pharmacokinetics of vinorelbine.

Warfarin: A single 125 mg dose of 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 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 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 the 3-day regimen of aprepitant with each chemotherapy cycle.

Tolbutamide: 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 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 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 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 aprepitant may be reduced. Alternative or back-up methods of contraception should be used during treatment with aprepitant and for 1 month following the last dose of aprepitant.

Midazolam: Aprepitant increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was co-administered on Day 1 and Day 5 of a regimen of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these agents with aprepitant.

In another study with intravenous administration of midazolam, aprepitant was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3-day regimen of aprepitant and on Days 4, 8, and 15. Aprepitant increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of aprepitant on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

An additional study was completed with intravenous administration of midazolam and aprepitant. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of aprepitant 125 mg. The plasma AUC of midazolam was increased by 1.5fold. This effect was not considered clinically important.

<u>Effect of other agents on the pharmacokinetics of aprepitant</u>

Aprepitant is a substrate for CYP3A4; therefore, co-administration of aprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of aprepitant 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, co-administration of aprepitant with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant.

Ketoconazole: When a single 125 mg dose of 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 aprepitant with strong CYP3A4 inhibitors should be approached cautiously.

Rifampin: When a single 375 mg dose of 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. Co-administration of aprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of aprepitant.

Additional interactions

Diltiazem: In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate, or blood pressure beyond those changes induced by diltiazem alone.

Paroxetine: Co-administration 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

Pregnancy

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

Breast-feeding mothers

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 Pediatric Use

Safety and effectiveness of aprepitant in pediatric patients have not been established.

4.8 Use in the Elderly

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.

4.9 Side Effects

The overall safety of aprepitant was evaluated in approximately 6500 individuals.

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

Highly Emetogenic Chemotherapy (HEC)

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. Aprepitant was given in combination with ondansetron and dexamethasone (aprepitant regimen) 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 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 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 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 aprepitant and HEC, the adverse experience profile was generally similar to that seen in the other HEC studies with aprepitant.

Moderately Emetogenic Chemotherapy (MEC)

In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), 868 patients were treated with aprepitant during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, aprepitant was given in combination with ondansetron and dexamethasone (aprepitant regimen) 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 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 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 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 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.

Other Studies
Single 40 mg doses of aprepitant have also been studied for the prevention of postoperative 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, dyspnoea, 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 serious adverse experiences 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 of aprepitant. 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

4.10 Overdose
No specific information is available on the treatment of overdosage with aprepitant. Single doses up to 600 mg of aprepitant were generally well tolerated in healthy subjects. 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, aprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective.

Aprepitant cannot be removed by hemodialysis.

5. CLINICAL PHARMACOLOGY

5.1 Mechanism of Action

Aprepitant 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 targets for existing CINV therapies.

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-HT_3-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

5.2 Pharmacokinetics

Absorption

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26% greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state.

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} was approximately 19.5 mcg• hr/mL and 20.1 mcg• hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1.5 mcg/mL and 1.4 mcg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

Distribution

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.

Metabolism

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.

Elimination

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 plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Characteristics in Patients

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 for aprepitant 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 for aprepitant is necessary in elderly patients.

Pediatric

The pharmacokinetics of aprepitant have not been evaluated in patients below 18 years of age.

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 for aprepitant 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

Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125 mg dose of 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 (Child-Pugh 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 for aprepitant 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 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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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 for aprepitant is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing hemodialysis.

6. INFORMATION FOR PATIENTS

Physicians should instruct their patients to read the patient package insert before starting therapy with aprepitant and to reread it each time the prescription is renewed.

Patients should be instructed to take aprepitant only as prescribed. Patients should be advised to take their first dose (125 mg) of aprepitant 1 hour prior to chemotherapy treatment.

Aprepitant may interact with some drugs including chemotherapy; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription 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 the 3-day regimen of aprepitant with each chemotherapy cycle.

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

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Hypromellose 2910, Poloxamer 407, Purified Water, Sucrose, Cellulose (microcrystalline), Gelatin, Sodium laurilsulfate, Titanium dioxide (E171, CI 77891), Shellac glaze~45% (20% esterified) in ethanol, Isopropyl alcohol, Iron oxide black (E172, CI 77499), N-butyl alcohol, Propylene glycol (E1520) and Ammonia solution, concentrated.
The 125mg capsules also contain Iron oxide Red (E172, CI 77491)

7.2 Shelf-life

Refer to outer carton

7.3 Special precautions for storage

Store below 30^0C.

7.4 Nature and contents of container

INAPITANT TRI-PACK CAPSULE are available in cartons of 3’s.

Name and Country of Manufacturer
PHARMATHEN INTERNATIONAL S.A
Industrial Park Sapes
Rodopi Prefecture
Block No 5
Rodopi 69300
Greece

This Package Insert was last revised in June 2021.