Relipitant™

RELIC
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For the use only of a Registered Medical Practitioner

Aprepitant Capsules IP

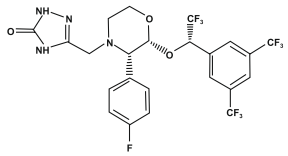
Relipitant™ 125 80
CAPSULES

GENERIC NAME
Aprepitant Capsules

COMPOSITION
Pack contains:
One capsule of **Relipitant** (Aprepitant 125 mg) & Two capsules of **Relipitant** (Aprepitant 80 mg)

Relipitant(Aprepitant 125 mg) **(1 capsule)**	**Relipitant**(Aprepitant 80 mg) **(2 capsules)**
Each hard gelatin capsule contains	Each hard gelatin capsule contains
Aprepitant ..... IP..... 125 mg	Aprepitant ..... IP..... 80 mg
Excipients..... q.s.	Excipients..... q.s.

DESCRIPTION[1]
Relipitant contains aprepitant, which is a substance P/neurokinin 1 (NK_1) receptor antagonist, chemically described as 5-([(2 *R*,3 5)-2-[(1 R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyllmethyl]-l,2-dihydro-3 H-l,2,4-triazol-3-one. Its empirical formula is $C_{23}H_{21}F_7N_4O_3$ with a molecular weight of 534.43. Its structural formula is:



INDICATIONS
Relipitant are indicated for the treatment of adult patients with chemotherapy induced nausea and vomiting (emesis).

DOSE AND METHOD OF ADMINISTRATION[1,2]
Relipitant are given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist.
The recommended dose of **Relipitant** (Aprepitant capsules) is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.
General Information
Chronic continuous administration is not recommended.
Relipitant may be taken with or without food.
No dosage adjustment is necessary for the elderly.
No dosage adjustment is necessary for patients with renal insufficiency 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).

USE IN SPECIAL POPULATIONS[1]
Pregnancy
Teratogenic Effects: Category B
Teratology studies have been performed in rats at oral doses up to 1000 mg/kg twice daily (plasma $AUC_{0\text{-}24hr}$ of 31.3 mcg•hr/mL about 1.6 times the human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma $AUC_{0\text{-}24hr}$ of 26.9 mcg•hr/mL about 1.4 times the human exposure at the recommended dose) and have revealed no evidence of impaired fertility or harm to the fetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Lactation
Aprepitant is excreted in the milk of 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 potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, 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.
Pediatrics
Safety and effectiveness of aprepitant in pediatric patients have not been established.
Geriatrics
In 2 well-controlled chemotherapy-induced nausea and vomiting clinical studies, of the total number of patients (N=544) treated with aprepitant, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

CONTRAINDICATIONS[1]
Relipitant are weak-to-moderate (dose-dependant) CYP3A4 inhibitor. They should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependant 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.
Relipitant are contraindicated in patients who are hypersensitive to any component of the product.

WARNINGS[1]
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.

PRECAUTIONS[1]
General
Aprepitant, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Moderate inhibition of CYP3A4 by aprepitant, 125 mg/80 mg regimen, could result in elevated plasma concentrations of these concomitant medicinal products.
Weak inhibition of CYP3A4 by a single 40 mg dose of aprepitant is not expected to alter the plasma concentrations of concomitant medicinal products that are primarily metabolized through CYP3A4 to a clinically significant degree.
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.
Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, aprepitant (125 mg/80 mg regimen) was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.
In a separate pharmacokinetic study in patients receiving docetaxel, which is also metabolized by CYP3A4, aprepitant (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.
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.
Coadministration 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.
Upon coadministration with aprepitant, the efficacy of hormonal contraceptives during and for 28 days following the last dose 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.
There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). Therefore, caution should be exercised when aprepitant is administered in these patients.
Information for patients
Physicians should instruct their patients to read the patient package insert before starting therapy with aprepitant capsules and to reread it each time the prescription is renewed.
Patients should be instructed to take aprepitant capsules only as prescribed. For the prevention of chemotherapy induced nausea and vomiting, patients should be advised to take their first dose (125 mg) of aprepitant capsule 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, 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 the 3-day regimen of aprepitant capsules 125 mg/80 mg with each chemotherapy cycle. 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 capsules and for 1 month following the last dose of aprepitant capsules.
Carcinogenesis, Mutagenesis, Impairment of Fertility[1]
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 1000 mg/kg twice daily. The highest dose produced a systemic exposure to aprepitant (plasma AUC0-24hr) of 0.7 to 1.6 times the human exposure ($AUC_{0\text{-}24hr}$ = 19.6 mcghr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 1000 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 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.
Aprepitant was 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.
Aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

DRUG INTERACTIONS[1]
Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Effect of aprepitant on the pharmacokinetics of other agents
Weak inhibition of CYP3A4 by a single 40 mg dose of aprepitant is not expected to alter the plasma concentrations of concomitant medicinal products that are primarily metabolized through CYP3A4 to a clinically significant degree. However, higher aprepitant doses or repeated dosing at any aprepitant dose may have a clinically significant effect.
As a moderate inhibitor of CYP3A4 at a dose of 125 mg/80 mg, aprepitant can increase plasma concentrations of concomitantly administered oral medicinal products that are metabolized through CYP3A4. For a given drug of CYP3A4 substrate, aprepitant 125 mg/80 mg may increase its plasma concentrations to a lesser extent when it is given intravenously rather than orally.
Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration 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-HT3 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 coadministered orally as 20 mg on Day 1, and aprepitant when given as 80 mg/day with dexamethasone coadministered 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 oral dexamethasone doses should be reduced by approximately 50% when coadministered with aprepitant (125 mg/80 mg regimen), 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. A single dose of aprepitant (40 mg) when coadministered with a single oral dose of dexamethasone 20 mg, increased the AUC of dexamethasone by 1.45-fold. Therefore, no dose adjustment is recommended.
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 1.34-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. The IV methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with aprepitant (125 mg/80 mg regimen) to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant. Although the concomitant administration of methylprednisolone with the single 40 mg dose of aprepitant has not been studied, a single 40 mg dose of aprepitant produces a weak inhibition of CYP3A4 (based on midazolam interaction study) and it is not expected to alter the plasma concentrations of methylprednisolone to a clinically significant degree. Therefore, no dose adjustment is recommended.

Chemotherapeutic agents:
Docetaxel: In a pharmacokinetic study, aprepitant (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.
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 daily dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21, and aprepitant was given as a 3-day 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 coadministration of aprepitant may reduce the efficacy of hormonal contraceptives during and for 28 days after administration of the last dose of aprepitant. Alternative or backup methods of contraception should be used during treatment with aprepitant and for 1 month following the last dose of aprepitant. While studies have not been done with the 40 mg single PONV dose, the timing of aprepitant administration relative to ovulation could cause contraceptive failure. Thus, patients should be instructed to use alternative or back-up methods of contraception 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 coadministered 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 coadministering these agents with aprepitant (125 mg/80 mg). A single dose of aprepitant (40 mg) increased the AUC of midazolam by 1.2-fold on Day 1, when a single oral dose of midazolam 2 mg was coadministered on Day 1 with aprepitant 40 mg; this effect was not considered clinically important.
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 1.5-fold. Depending on clinical situations (e.g. elderly patients) and degree of monitoring available, dosage adjustment for intravenous midazolam may be necessary when it is coadministered with aprepitant for the chemotherapy induced nausea and vomiting indication (125 mg Day 1 followed by 80 mg on Days 2 and 3).

Effect of other agents on the pharmacokinetics of aprepitant
Aprepitant is a substrate for CYP3A4; therefore, coadministration 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 with caution. 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 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. Coadministration 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: 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.

UNDESIRABLE EFFECTS[1]
The overall safety of aprepitant capsules was evaluated in approximately 4400 individuals.

Chemotherapy Induced Nausea and Vomiting
Highly Emetogenic Chemotherapy
In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 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 and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.
In Cycle 1, clinical adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 68% of patients treated with standard therapy. Table 1 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 1: Percent of Patients Receiving Highky Emetogenic Chemotherapy with Clinical Adverse Experiences (Incidence ≥3%) Cycle 1

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
Body as a Whole/Site Unspecified		
Abdominal Pain	4.6	3.3
Asthenia/Fatigue	17.8	11.8
Dehydration	5.9	5.1
Dizziness	6.6	4.4
Fever	2.9	3.5
Mucous Membrane Disorder	2.6	3.1
Digestive System		
Constipation	10.3	12.2
Diarrhea	10.3	7.5
Epigastric Discomfort	4.0	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
Eyes, Ears, Nose, and Throat		
Tinnitus	3.7	3.8
Hemic and Lymphatic System		
Neutropenia	3.1	2.9
Metabolism and Nutrition		
Anorexia	10.1	9.5
Nervous System		
Headache	8.5	8.7
Insomnia	2.9	3.1
Respiratory System		
Hiccups	10.8	5.6

In addition, isolated cases of serious adverse experiences, regardless of causality, of bradycardia, disorientation, and perforating duodenal ulcer were reported in highly emetogenic CINV clinical studies.

Moderately Emetogenic Chemotherapy
During Cycle 1 of a moderately emetogenic chemotherapy study, 438 patients were treated with the aprepitant regimen and 385 of these patients continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. In Cycle 1, clinical adverse experiences were reported in approximately 73% of patients treated with the aprepitant regimen compared with approximately 75% of patients treated with standard therapy.
The adverse experience profile in the moderately emetogenic chemotherapy study was generally comparable to the highly emetogenic chemotherapy studies. Table 2 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 2: Percent of Patients Receiving Moderately Emetogenic Chemotherapy with Clinical Adverse Experiences (Incidence ≥3%) - Cycle 1

	Aprepitant Regimen (N = 438)	Standard Therapy (N = 428)
Body and Lymphatic System Disorders		
Neutropenia	8.9	8.4
Metabolism and Nutritional Disorders		
Anorexia	4.3	5.8
Psychiatric Disorders		
Insomnia	4.1	5.6
Nervous System Disorders		
Dizziness	3.4	4.2
Headache	16.4	16.4
Anorexia		
Vascular Disorders		
Hot Flush	3.0	1.4
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	3.0	2.3
Gastrointestinal Disorders		
Constipation	12.3	18.0
Diarrhea	5.5	6.3
Dyspepsia	8.4	4.9
Nausea	7.1	7.5
Stomatitis	5.3	4.4
Skin and Subcutaneous Tissues Disorders		
Alopecia	24.0	22.2
General Disorders and General Administration Site Conditions		
Asthenia	3.4	3.7
Fatigue	21.9	21.5
Mucosal inflammation	2.5	3.5

Isolated cases of serious adverse experiences, regardless of causality, of dehydration, enterocolitis, febrile neutropenia, hypertension, hypoesthesia, neutropenic sepsis, pneumonia, and sinus tachycardia were reported in the moderately emetogenic CINV clinical study.

Highly and Moderately Emetogenic Chemotherapy
The following additional clinical adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen:
Infections and infestations: candidiasis, herpes simplex, lower respiratory infection, pharyngitis, septic shock, upper respiratory infection, urinary tract infection.
Neoplasms benign, malignant and unspecified (including cysts and polyps): malignant neoplasm, nonsmall cell lung carcinoma.
Blood and lymphatic system disorders: anemia, febrile neutropenia, thrombocytopenia.
Metabolism and nutrition disorders: appetite decreased, diabetes mellitus, hypokalemia.
Psychiatric disorders: anxiety disorder, confusion, depression.
Nervous system: peripheral neuropathy, sensory neuropathy, taste disturbance, tremor.
Eye disorders: conjunctivitis.
Cardiac disorders: myocardial infarction, palpitations, tachycardia.
Vascular disorders: deep venous thrombosis, flushing, hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, nasal secretion, pneumonitis, pulmonary embolism, respiratory insufficiency, vocal disturbance.
Gastrointestinal disorders: acid reflux, deglutition disorder, dry mouth, dysgeusia, dysphagia, eructation, flatulence, obstipation, salivation increased.
Skin and subcutaneous tissue disorders: acne, diaphoresis, rash.
Musculoskeletal and connective tissue disorders: arthralgia, back pain, muscular weakness, musculoskeletal pain, myalgia.
Renal and urinary disorders: dysuria, renal insufficiency.
Reproductive system and breast disorders: pelvic pain.
General disorders and administrative site conditions: edema, malaise, rigors.
Investigations: weight loss
Laboratory Adverse Experiences
Table 3 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% in patients receiving highly emetogenic chemotherapy.

Table 3: Percent of Patients Receiving Highly Emetogenic Chemotherapy with Laboratory Adverse Experiences (Incidence ≥3%) - Cycle 1

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
ALT increased	6.0	4.3
AST increased	3.0	1.3
Blood Urea Nitrogen Increased	4.7	3.5
Serum Creatinine Increased	3.7	4.3
Proteinuria	6.8	5.3

The following additional laboratory adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen: alkaline phosphatase increased, hyperglycemia, hyponatremia, leukocytes increased, erythrocyturia, leukocyturia.
The adverse experiences of increased AST and ALT were generally mild and transient.
The following laboratory adverse experiences were reported at an incidence ≥3% during Cycle 1 of the moderately emetogenic chemotherapy study in patients treated with the aprepitant regimen or standard therapy, respectively: decreased hemoglobin (2.3%, 4.7%) and decreased white blood cell count (9.3%, 9.0%).
The adverse experience profiles in the Multiple-Cycle extensions for up to 6 cycles of chemotherapy were generally similar to that observed in Cycle 1.
Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy in another CINV study.

OVERDOSAGE[1]
No specific information is available on the treatment of overdosage with aprepitant capsules. 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 sdaily 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.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES[1,2]
- **Mechanism of Action**

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

- **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 bioavilabillity of aprepitant. The pharmacokinetics of aprepitant are non-linear across the clinical dose range.
Distribution
Aprepitant is more than 95% bound to plasma proteins.
The mean apparent volume of distribution at steady state (Vdss) is approximately 70 L in humans. Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans.
Metabolism
Aprepitant undergoes extensive metabolism. Aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.
Excretion
Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent plasma clearance of aprepitant ranged from approximately 62 to 90 mL /min. The apparent terminal half-life ranged from approximately 9 to 13hours.
Pharmacokinetics in Special Populations
Gender
No dosage adjustment for aprepitant is necessary based on gender.
Geriatric
No dosage adjustment for aprepitant is necessary in elderly patients.
Pediatric
The pharmacokinetics of aprepitant have not been evaluated in patients below 18years of age.
Race
No dosage adjustment for aprepitant is necessary based on race.
Hepatic Insufficiency
Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. 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
No dosage adjustment for aprepitant is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.

INCOMPATIBILITES
None

SHELF LIFE
24 months

PACKAGING INFORMATION **Relipitant** is available as one capsule of 125 mg + 2 capsules of 80 mg per kit pack

STORAGE AND HANDLING INSTRUCTIONS
Store protected from light & moisture, at a temperature not exceeding 30°C.

KEEP OUT OF REACH OF CHILDREN