Aprepet-Z Aprepitant Capsules

Composition

Pack contains:

One capsule of Aprepitant 125 mg &

Two capsules of Aprepitant 80 mg

APREPET-Z 80

Each hard gelatin capsule contains

Aprepitant 80 mg.

Excipients q.s.

Empty gelatin capsule contains approved colours.

APREPET-Z 125

Each hard gelatin capsule contains

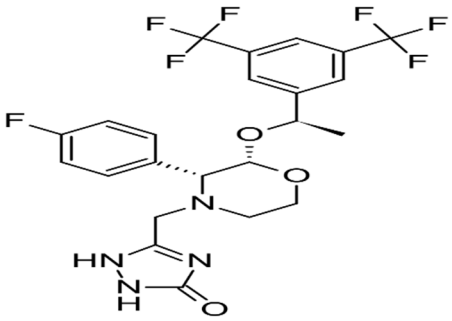
Aprepitant 125 mg.

Excipients q.s.

Empty gelatin capsule contains approved colours.

Description

Aprepitant is a substance p/neurokinin 1 (NK1) receptor antagonist, chemically described as 5-[[(2 R,3 S)-2-[(1 r)-1-[3,5-BIS (TRIFLUOROMETHYL) PHENYL] ETHOXY] -3-(4-fluorophenyl)-4-morpholinyl] methyl]-1,2-dihydro-3 H-1,24-triazol-3-one. Its empirical formula is C23H21F7N4O3, and its structural formula is :



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl Clinical Pharmacology.

Pharmacodynamics:

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).

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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 Emision 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 (Cmax) of aprepitant occurred at approximately 4 hours (Tmax). 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.

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 CYP2C 19. 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 13 hours.

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 18 years 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.

INDICATIONS AND USAGE: Aprepitant, for the treatment of adult patients with chemotherapy induced nausea and vomiting.

DOSAGE AND ADMINISTRATION :

Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose of aprepitant is 125mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.

PRECAUTIONS:

General :

Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally adinistered CYP3A4 substrates is expected to be 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 was administered commonly with etoposide, vinorelbine, or paclitaxel. The dose of these agents were not adjusted to account for potential drug interactions.

Due to the small number of patients in clinical studies who received the CYP3A4 substrate docetaxel, 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.

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.

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 7-10 days, following initiation of the 3 day regimen of aprepitant with each chemotherapy cycle.

The efficacy of oral contraceptives during administration of aprepitant may be reduced. Although effects on contraception with a 3 day regimen of aprepitant given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used.

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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility :

Three 2 years carcinogenicity studies of aprepitant (Two in Sprague-Dawley rats and one in CD-1 mice) were conducted with aprepitant. Dose selection for the studies was based on saturation of absorption in both species. In the rat carcinogenicity studies, animals were treated with oral doses of 0.05. 0.25, 1,5,25, 125 mg/kg twice daily. The highest dose tested produced a systemic exposure to aprepitant [plasma AUC (0-24TH)] of 0.4-1.4 times the human exposure [AUC (0-24 H)= 19.6 ug-h/ml] at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5-125mg/kg twice per day produced thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced increased incidences of hepatocellular adenoma at 25 and 125 mg/kg twice daily, and thyroid follicular adenoma at the 125 mg /kg twice daily dose. In the mouse carcinogenicity study, animals were treated with oral doses of 2.5, 25, 125, and 500 mg/kg/day. The highest tested dose produced a systemic exposure of about 2.2-2.7 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas in male mice of 125 and 500 mg/kg/day groups.

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).

Pregnancy, Teratogenic Effects, Pregnancy Category B:

Teratology studies have been performed in rats at oral doses up to 1000mg./kg twice daily [plasma AUC (0-24h) of 31.3 ug-h/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 (0-24 h) of 26.9 ug-h/ml, about 1.4 times the human exposure at the recommended dose] and have received 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.

WARNINGS:

Nursing Mothers

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.

Pediatric Use

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

Geriatric Use

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.

Adverse Reactions:

Aprepitant may produce Asthenia/Fatigue, Dehydration, Abdominal Pain, Dizziness, Constipation, Diarrhea, Epigastric Discomfort, Gastritis, Anorexia, Headache, Alopecia.

Isolated cases of serious adverse experiences like dehydration, enterocolitis, febrile neutropenia, hypertension, hypoesthesia, neutropenic sepsis, pneumonia, and sinus tachycardia acne, diaphoresis, rash.

Laboratory Adverse reports were increase in AST/ALT were generally mild and transient., BUN, Sr. Creatine, Proteinuria.

DRUG INTERACTIONS:

Aprepitant is a substrate, a moderate inhibitor, and an induceof CYP3A4.

Aprepitant is also an inducer of CYP2C9.

5-HT3 antagonists: In clinical drug ineraction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granistron, or hydrodolasetron (the active metabolite of do[asetron).

Corticosteroids:

Dexamethasone- The oral dexamethasone doses should be reduced by approximately 50% when coadministered with Aprepitant, to achieve exposures of dexamethasone similar to those obtained when it is given without Aprepitant.

Methylprednisolone- The IV & Oral methylprednisolone dose should be reduced by approximately 25% and 50% when coadministered with to Aprepitant. Therefore, dose need to be adjusted.

Docetaxel: In a pharmacokinetic study. Aprepitant did not influence the pharmacokinetics of docetaxel.

Warfarin: 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.

Oral Contraceptives: The coadministration of Aprepitant 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

Overdose:

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.

CONTRAINDICATIONS:

Aprepitant is a moderate CYP3A4 inhibitor. 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.

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

Storage: Store in a cool, dry place. Protect from light.

PRESENTATION:

Each pack contains:

One capsule of APREPET-Z 125 & Two capsules of APREPET-Z 80

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in