APREON

Aprepitant Capsules U.S.P. 40 mg, 80 mg and 125 mg

COMPOSITION

Apreon 40mg capsule contains: Aprepitant U.S.P. ..... 40 mg
Apreon 80mg capsule contains: Aprepitant U.S.P. ..... 80 mg
Apreon 125mg capsule contains: Aprepitant U.S.P. ..... 125 mg

Apreon Combo Pack contains: 2 capsules of Aprepitant 80mg & 1 capsule of Aprepitant 125mg

DRUG DESCRIPTION

Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist, chemically described as 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis (trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl] methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one.Its empirical formula is C23H21F7N4O3 with a molecular weight of 534.43.

CLINICAL PHARMACOLOGY

Prevents acute and delayed vomiting by inhibiting the substance P/neurokinin 1 (NK1) receptor; augments the antiemetic activity of 5-HT3 receptor antagonists and corticosteroids to inhibit acute and delayed phases of chemotherapy-induced emesis.

Pharmacodynamics/Kinetics

Aprepitant displays non-linear pharmacokinetics. Both clearance and absolute bioavailability decrease with increasing dose.

Absorption

Cmax of aprepitant occurred at approximately 4 hours (tmax). 800 Kcal standard breakfast resulted in an up to 40 % increase in AUC of aprepitant.

Distribution: Vd: ~70 L; crosses the blood-brain barrier

Protein binding: >95%

Metabolism: Extensively hepatic via CYP3A4 (major); CYP1A2 and CYP2C19 (minor); forms 7 metabolites (weakly active)

Bioavailability: ~60% to 65%

Half-life elimination: Terminal: ~9-13 hours

Time to peak, plasma: ~3-4 hours.

Elimination: Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. The plasma clearance of aprepitant is dose-dependent, decreasing with increased dose and ranged from approximately 60 to 72 ml/min in the therapeutic dose range.

INDICATIONS

1. Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults.
2. Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.
   Apreon 125 mg/80 mg is given as part of combination therapy
3. Prevention of Postoperative Nausea and Vomiting PONV
   The recommended oral dosage of APREON is 40 mg within 3 hours prior to induction of anesthesia.

Limitations of Use

APREON has not been studied for the treatment of established nausea and vomiting.
Chronic continuous administration is not recommended.

DOSAGE AND ADMINISTRATION:

Posology

APREON is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose is 125 mg orally once daily one hour before start of chemotherapy on Day 1 and 80 mg orally once daily on Days 2 and 3.
The following regimens are recommended for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy:

Highly Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3	Day 4
APREON	125mg orally	80mg orally	80mg orally	None
Dexamethasone	12mg orally	8mg orally	8mg orally	8mg orally
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists	None	None	None

Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 to 4. The dose of dexamethasone accounts for active substance interactions.

Moderately Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3
APREON	125mg orally	80mg orally	80mg orally
Dexamethasone	12mg orally	None	None
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists.	None	None

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

Prevention of Postoperative Nausea and vomiting The recommended oral dosage of APREON is 40 mg within 3 hours prior to induction of anesthesia.

Method of administration: The hard capsule should be swallowed whole. APREON may be taken with or without food.
PONV: Administer within 3 hours prior to induction; follow healthcare providers instructions about food/drink restrictions prior to surgery.

Dosing in Special Populations:

Older people (≥65 years): No dose adjustment is necessary for the elderly.

Gender: No dose adjustment is necessary based on gender.

Renal impairment: No dose adjustment is necessary for patients with renal impairment or for patients with end stage renal disease undergoing haemodialysis.

Hepatic impairment: No dose adjustment is necessary for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. Aprepitant should be used with caution in these patients.

Paediatric population: The safety and efficacy of Aprepitant in children and adolescents below 18 years of age has not yet been established. No data are available.

ADVERSE REACTIONS

Note: Adverse reactions reported as part of a combination chemotherapy regimen or with general anesthesia.

>10%: Central nervous system: Fatigue (≤18%), Gastrointestinal: Nausea (6% to 13%), constipation (9% to 10%), Neuromuscular & skeletal: Weakness (≤18%), Miscellaneous: Hiccups (11%)

1% to 10%: Cardiovascular: Hypotension (≤6%), bradycardia (≤4%), Central nervous system: Dizziness (≤7%), Endocrine & metabolic: Dehydration (≤6%), Gastrointestinal: Diarrhea (≤10%), dyspepsia (≤6%), abdominal pain (≤5%), epigastric discomfort (4%), gastritis (4%), stomatitis (3%)
Hepatic: ALT increased (≤6%), AST increased (3%)
Renal: Proteinuria (7%), BUN increased (5%)

>0.5% (Limited to important or life-threatening): Acid reflux, acne, albumin decreased, alkaline phosphatase increased, anaphylactic reaction, anemia, angioedema, anxiety, appetite decreased, arthralgia, back pain, bilirubin increased, candidiasis, confusion, conjunctivitis, cough, deglutition disorder, depression, diabetes mellitus, diaphoresis, disorientation, duodenal ulcer (perforating), DVT, dysarthria, dysphagia, dyspnea, dysuria, edema, enterocolitis, eructation, erythrocyturia, febrile neutropenia, flatulence, flushing, glucosuria, herpes simplex, hyperglycemia, hypersensitivity reaction, hypertension, hypoesthesia, hypokalemia, hyponatremia, hypothermia, hypovolemia, hypoxia, leukocytes increased, leukocyturia, malaise, MI, miosis, muscular weakness, musculoskeletal pain, myalgia, nasal secretion, neutropenic sepsis, obstipation, pain, palpitation, pelvic pain, peripheral neuropathy, pharyngitis, pharyngolaryngeal pain, pneumonia, pneumonitis, pruritus, pulmonary embolism, rash, renal insufficiency, respiratory infection, respiratory insufficiency, rigors, salivation increased, sensory disturbance, sensory neuropathy, septic shock, Stevens-Johnson syndrome, syncope, tachycardia, taste disturbance, thrombocytopenia, toxic epidermal necrolysis, tremor, urinary tract infection, urticaria, visual acuity decreased, vocal disturbance, weight loss, wheezing, xerostomia

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- Co-administration with pimozide, terfenadine, astemizole or cisapride

WARNINGS/PRECAUTIONS

Disease-related concerns:

Hepatic impairment: Use with caution in patients with severe hepatic impairment (Child-Pugh class C); has not been studied.
Nausea/vomiting: Appropriate use: Not studied for treatment of existing nausea and vomiting. Chronic continuous administration is not recommended.

Concurrent drug therapy issues:

Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

Other warnings/precautions:

Contraception in males and females: The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of APREON. Alternative non-hormonal back-up methods of contraception should be used during treatment with APREON and for 2 months following the last dose of APREON.

Pregnancy: Risk Category B. APREON should not be used during pregnancy unless clearly necessary.

Breast-feeding: Breast-feeding is not recommended during treatment with APREON.

Fertility

Fertility studies did not indicate direct or indirect harmful effects with respect to mating performance, fertility, embryonic / fetal development, or sperm count and motility

DRUG INTERACTIONS

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

CYP3A4 Substrates: As a moderate inhibitor of CYP3A4 at a dose of 125 mg/80 mg, aprepitant can increase plasma concentrations of concomitantly administered oral medications that are metabolized through CYP3A4.

5-HT3 antagonists: aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids: 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.

Chemotherapeutic agents: Aprepitant (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel & Vinorelbine.

CYP2C9 Substrates (Warfarin, Tolbutamide, Phenytoin): Coadministration of drugs that are known to be metabolized by CYP2C9 may result in lower plasma concentrations of these drugs.

Midazolam: 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 APREON (125 mg/80 mg).

Effect of Other Agents on the Pharmacokinetics of Aprepitant

Aprepitant is a substrate for CYP3A4; therefore, concomitant administration of APREON 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 APREON 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 APREON.

Shelf Life: 2 Years

Storage: Do not store above 30°C.

Instructions

Keep away from moisture, heat, light and children.
To be dispensed on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:
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