Capsule

NAUTANT

(Aprepitant)

نوٹینٹ کیپسول

(اپرپٹینٹ)

COMPOSITION

Nautant Capsule 80mg

Each capsule contains:

Aprepitant.....80mg

(USP Specifications)

Nautant Capsule 125mg

Each capsule contains:

Aprepitant.....125mg

(USP Specifications)

DESCRIPTION

Aprepitant, an antiemetic, is a substance P/neurokinin 1 (NK_1) receptor antagonist which, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV).

MECHANISM OF ACTION

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), 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 NK_1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the $5\text{-}HT_3$ receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

INDICATIONS

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Aprepitant, in combination with other antiemetic agents, is indicated for the: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Prevention of Postoperative Nausea and Vomiting (PONV)

Aprepitant is indicated for the prevention of postoperative nausea and vomiting.

Limitations of Use

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

DOSAGE & ADMINISTRATION

Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a $5\text{-}HT_3$ 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 in the morning.

Adults

The following regimens are recommended in adults for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy:

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

Pediatrics

Adolescents (aged 12 through 17 years)

Aprepitant is given for 3 days as part of a regimen that includes a $5\text{-}HT_3$ antagonist. The recommended dose of capsules of Aprepitant is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. Aprepitant is administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, Aprepitant should be administered in the morning.

If a corticosteroid, such as dexamethasone, is co-administered with Aprepitant, the dose of the corticosteroid should be administered at 50 % of the usual dose. The safety and efficacy of the aprepitant 80 mg and 125 mg capsules have not been demonstrated in children less than 12 years of age. No data are available.

General

Efficacy data in combination with other corticosteroids and $5\text{-}HT_3$ antagonists are limited.

Renal impairment

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

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.

Highly Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3	Day 4
Aprepitant	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
$5\text{-}HT_3$ antagonists	Standard dose of $5\text{-}HT_3$ antagonists. See the product information for the selected $5\text{-}HT_3$ 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 to 4. The dose of dexamethasone accounts for active substance interactions.

Moderately Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3
Aprepitant	125 mg orally	80 mg orally	80 mg orally
Dexamethasone	12 mg orally	none	none
$5\text{-}HT_3$ antagonists	Standard dose of $5\text{-}HT_3$ antagonists. See the product information for the selected $5\text{-}HT_3$ antagonist for appropriate dosing information	none	none

PHARMACODYNAMICS

NK_1 Receptor Occupancy

In two single-blind, multiple-dose, randomized, and placebo control studies, healthy young men received oral aprepitant doses of 10 mg (N=2), 30 mg (N=3), 100 mg (N=3) or 300 mg (N=5) once daily for 14 days with 2 or 3 subjects on placebo. Both plasma aprepitant concentration and NK_1 receptor occupancy in the corpus striatum by positron emission tomography were evaluated, at predose and 24 hours after the last dose. At aprepitant plasma concentrations of ~10 ng/mL and ~100 ng/mL, the NK_1 receptor occupancies were ~50% and ~90%, respectively. The oral aprepitant regimen for CINV produces mean trough plasma aprepitant concentrations >500 ng/mL, which would be expected to, based on the fitted curve with the Hill equation, result in >95% brain NK_1 receptor occupancy. However, the receptor occupancy for either CINV or PONV dosing regimen has not been determined. In addition, the relationship between NK_1 receptor occupancy and the clinical efficacy of aprepitant has not been established.

Cardiac Electrophysiology

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

QT prolongation with the oral dosing regimens for CINV and PONV are not expected.

PHARMACOKINETICS

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

Absorption

The mean absolute oral bioavailability of aprepitant is 67 % for the 80 mg capsule and 59 % for the 125 mg capsule. The mean peak plasma concentration C_{max} of aprepitant occurred at approximately 4 hours (T_{max}). Oral administration of the capsule with an approximately 800 Kcal standard breakfast resulted in an up to 40 % increase in AUC of aprepitant. This increase is not considered clinically relevant.

The pharmacokinetics of aprepitant is non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0\text{-}\infty}$ 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 $AUC_{0\text{-}24hr}$ (mean±SD) was 19.6 ± 2.5 µgh/mL and 21.2 ± 6.3 µg h/mL on Days 1 and 3, respectively. C_{max} was 1.6 ± 0.36 µg/mL and 1.4 ± 0.22 µg/mL on Days 1 and 3, respectively.

Distribution

Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean apparent volume of distribution at steady state (Vdss) is approximately 66 L in humans.

Biotransformation

Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 19 % of the radioactivity in plasma over 72 hours following a single intravenous administration 100mg dose of [14C]-fosaprepitant, a prodrug for aprepitant, indicating a substantial presence of metabolites in the plasma. Twelve metabolites of aprepitant have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains and the resultant metabolites were only weakly active. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 and potentially with minor contribution by CYP1A2 and CYP2C19.

Elimination

Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. Following a single intravenously administered 100 mg dose of [14C]-fosaprepitant, a prodrug for aprepitant, to healthy subjects, 57 % of the radioactivity was recovered in urine and 45 % 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. The terminal half-life ranged from approximately 9 to 13 hours.

ADVERSE REACTIONS

System organ class	Adverse reaction	Frequency
Infection and infestations	candidiasis, staphylococcal infection	rare
Blood and lymphatic system disorders	febrile neutropenia, anaemia	uncommon
Immune system disorders	hypersensitivity reactions including anaphylactic reactions	not known
Metabolism and nutrition disorders	decreased appetite	common
	polydipsia	rare
Psychiatric disorders	anxiety	uncommon
	disorientation, euphoric mood	rare
Nervous system disorders	headache	common
	dizziness, somnolence	uncommon
	cognitive disorder, lethargy, dysgeusia	rare
Eye disorders	conjunctivitis	rare
Ear and labyrinth disorders	tinnitus	rare
Cardiac disorders	palpitations	uncommon
	bradycardia, cardiovascular disorder	rare
Vascular disorders	hot flush/flushing	uncommon
Respiratory, thoracic and mediastinal disorders	hiccups	common
	oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation	rare
Gastrointestinal disorders	constipation, dyspepsia	common
	eructation, nausea, vomiting, gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence	uncommon
	duodenal ulcer perforation, stomatitis, abdominal distension, faeces hard, neutropenic colitis	rare
Skin and subcutaneous tissue disorders	rash, acne	uncommon
	photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/toxic epidermal necrolysis	rare
	pruritus, urticaria	not known
Musculoskeletal and connective tissue disorders	muscular weakness, muscle spasms	rare
Renal and urinary disorders	dysuria	uncommon
	pollakiuria	rare
General disorders and administration site conditions	fatigue	common
	asthenia, malaise	uncommon
	oedema, chest discomfort, gait disturbance	rare
Investigations	ALT increased	common
	AST increased, blood alkaline phosphatase increased	uncommon
	red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present, urine output increased	rare

WARNINGS AND PRECAUTIONS

Patients with moderate to severe 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.

CYP3A4 interactions

APREPITANT should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, ergot alkaloid derivatives, fentanyl, and quinidine. Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination might result in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)

In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely during treatment with aprepitant and for 14 days following each 3-day course of aprepitant.

Co-administration with hormonal contraceptives

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

Pregnancy

For aprepitant no clinical data on exposed pregnancies are available. The potential for reproductive toxicity of aprepitant has not been fully characterised, since exposure levels above the therapeutic exposure in humans at the 125 mg/80 mg dose could not be attained in animal studies. These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition and postnatal development. The potential effects on reproduction of alterations in neurokinin regulation are unknown. Aprepitant should not be used during pregnancy unless clearly necessary.

Breast-feeding

Aprepitant is excreted in the milk of lactating rats. It is not known whether aprepitant is excreted in human milk; therefore, breast-feeding is not recommended during treatment with aprepitant.

Fertility

The potential for effects of aprepitant on fertility has not been fully characterized because exposure levels above the therapeutic exposure in humans could not be attained in animal studies. These fertility studies did not indicate direct or indirect harmful effects with respect to mating performance, fertility, embryonic/foetal development, or sperm count and motility.

DRUG INTERACTIONS

Aprepitant (125 mg/80 mg) is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with APREPITANT, CYP3A4 is inhibited. After the end of treatment, APREPITANT causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation. Aprepitant does not seem to interact with the P-glycoprotein transporter, as suggested by the lack of interaction of aprepitant with digoxin.

Effect of aprepitant on the pharmacokinetics of other active substances

CYP3A4 inhibition

As a moderate inhibitor of CYP3A4, aprepitant (125 mg/80 mg) can increase plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of orally administered CYP3A4 substrates may increase up to approximately 3-fold during the 3-day treatment with aprepitant; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. Aprepitant must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. Caution is advised during concomitant administration of aprepitant and orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine.

Corticosteroids

Dexamethasone: The usual oral dexamethasone dose should be reduced by approximately 50 % when co-administered with aprepitant 125 mg/80 mg regimen. The dose of dexamethasone in chemotherapy induced nausea and vomiting clinical trials was chosen to account for active substance interactions. 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, 2.2-fold on Days 1 and 5.

Methylprednisolone: The usual intravenously administered methylprednisolone dose should be reduced approximately 25 %, and the usual oral methylprednisolone dose should be reduced approximately 50 % when co-administered with aprepitant 125 mg/80 mg regimen. 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.

During continuous treatment with methylprednisolone, the AUC of methylprednisolone may decrease at later time points within 2 weeks following initiation of the aprepitant dose, due to the inducing effect of aprepitant on CYP3A4. This effect may be expected to be more pronounced for orally administered methylprednisolone.

Chemotherapeutic medicinal products

In pharmacokinetic studies, aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, did not influence the pharmacokinetics of docetaxel administered intravenously on Day 1 or vinorelbine administered intravenously on Day 1 or Day 8. Because 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, an interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g., etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolised primarily or partly by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration.

Immunosuppressants

During the 3-day CINV regimen, a transient moderate increase followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g., cyclosporine, tacrolimus, everolimus and sirolimus) is expected. Given the short duration of the 3-day regimen and the time-dependent limited changes in exposure, dose reduction of the immunosuppressant is not recommended during the 3 days of co-administration with aprepitant.

Midazolam

The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicinal products with aprepitant (125 mg/80 mg).

Aprepitant increased the AUC of midazolam, a sensitive CYP3A4 substrate, 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of 2 mg midazolam was co-administered on Days 1 and 5 of a regimen of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 to 5.

Induction

As a mild inducer of CYP2C9, CYP3A4 and glucuronidation, aprepitant can decrease plasma concentrations of substrates eliminated by these routes within two weeks following initiation and treatment. This effect may become apparent only after the end of a 3-day treatment with aprepitant. For CYP2C9 and CYP3A4 substrates, the induction is transient with a maximum effect reached 3-5 days after end of the aprepitant 3-day treatment. The effect is maintained for a few days, thereafter slowly declines and is clinically insignificant by two weeks after end of aprepitant treatment. Mild induction of glucuronidation is also seen with 80 mg oral aprepitant given for 7 days. Data are lacking regarding effects on CYP2C8 and CYP2C19. Caution is advised when warfarin, acenocoumarol, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered during this time period.

Warfarin

In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with aprepitant and for 2 weeks following each 3-day course of aprepitant for chemotherapy induced nausea and vomiting. When 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 stabilised on chronic warfarin therapy, there was no effect of aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3; however, there was a 34 % decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14 % decrease in INR 5 days after completion of treatment with aprepitant.

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.

Hormonal contraceptives

The efficacy of hormonal contraceptives may be reduced during and for 28

days after administration of aprepitant. Alternative non-hormonal back-up methods of contraception should be used during treatment with aprepitant and for 2 months following the last dose of aprepitant.

In a clinical study, single doses of an oral contraceptive containing ethinyl estradiol and norethindrone were 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 intravenously on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. During days 9 through 21 in this study, there was as much as a 64 % decrease in ethinyl estradiol trough concentrations and as much as a 60 % decrease in norethindrone trough concentrations.

5-HT$_3$ antagonists

In clinical interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of other medicinal products on the pharmacokinetics of aprepitant

Concomitant administration of aprepitant with active substances that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, and protease inhibitors) should be approached cautiously, as the combination is expected to result several-fold in increased plasma concentrations of aprepitant.

Concomitant administration of aprepitant with active substances 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 that may result in decreased efficacy of aprepitant. Concomitant administration of aprepitant with herbal preparations containing St. John's Wort *(Hypericum perforatum)* is not recommended.

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.

Rifampicin

When a single 375 mg dose of 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 91 % and the mean terminal half-life decreased 68 %.

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, emesis induced by a medicinal product may not be effective.

Aprepitant cannot be removed by haemodialysis.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with pimozide, terfenadine, astemizole or cisapride.

STORAGE & INSTRUCTIONS

Store below 30°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

Nautant Capsule 80mg

2 capsules.

Nautant Capsule 125mg

1 capsule.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دھوپ، گرمی اور نمی سے بچائیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔ بچوں کی پہنچ سے دور رکھیں۔

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