1 APREPITANT 40 mg, 80 mg, and 125 mg CAPSULE (Alchemy)

Aprepitant 40 mg, 80 mg, and 125 mg capsule

NOTE: Only the 80mg strength is currently available

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 40 mg capsule contains 40 mg of aprepitant
Each 80 mg capsule contains 80 mg of aprepitant
Each 125 mg capsule contains 125 mg of aprepitant

Excipients with known effect
Each 40 mg capsule contains 40 mg of sucrose and 0.00013 mmol (0.003 mg) of sodium.
Each 80 mg capsule contains 80 mg of sucrose and 0.00022 mmol (0.005 mg) of sodium.
Each 125 mg capsule contains 125 mg of sucrose and 0.00026 mmol (0.006 mg) of sodium.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

40 mg: A size #4 opaque, hard gelatin capsule with white body and yellow cap with “40 mg” printed on the body in black ink.

80 mg: A size #2 opaque, hard gelatin capsule with white body and white cap with “80 mg” printed on the body in black ink.

125 mg: A size #1 opaque, hard gelatin capsule with white body and pink cap with “125 mg” printed on the body in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aprepitant (Alchemy), 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 (see Section 4.2)
- moderately emetogenic cancer chemotherapy (see Section 4.2).

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

4.2 Dose and method of administration

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

Aprepitant (Alchemy) is available as capsules for oral administration.

Aprepitant (Alchemy) is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The data sheet for the co-administered 5-HT_3 antagonist (e.g., ondansetron) must be consulted prior to initiation of treatment with Aprepitant (Alchemy).

The recommended dose of Aprepitant (Alchemy) for the 3-day oral regimen 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.

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

	Day 1	Day 2	Day 3	Day 4
Aprepitant (Alchemy)	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 (e.g., ondansetron)	See the data sheet 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 medicine interactions.

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

	Day 1	Day 2	Day 3
Aprepitant (Alchemy)	125 mg orally	80 mg orally	80 mg orally
Dexamethasone*	12 mg orally	none	none
5-HT_3 antagonist (e.g., ondansetron)	See the data sheet 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 was chosen to account for medicine interactions.

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

The recommended oral dosage of Aprepitant (Alchemy) is 40 mg within 3 hours prior to induction of anaesthesia.

Method of administration

Capsules should be swallowed whole.

General information

See Section 4.5 for additional information on the administration of Aprepitant (Alchemy) with corticosteroids.

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

Aprepitant (Alchemy) 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 haemodialysis.

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).

Paediatric patients

The safety and efficacy of aprepitant in paediatric patients have not been established.

4.3 Contraindications

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

Aprepitant (Alchemy) should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see Section 4.5).

4.4 Special warnings and precautions for use

Aprepitant, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolised through CYP3A4; some chemotherapy agents are metabolised by CYP3A4 (see Section 4.5). Moderate inhibition of CYP3A4 by aprepitant, 125 mg/80 mg 3-day oral regimen, could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see Section 4.5). Weak inhibition of CYP3A4 by a single 40 mg dose of aprepitant is not expected to alter the plasma concentrations of these concomitant medicinal products 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 (see Section 4.5).

Co-administration of aprepitant with warfarin may result in a clinically significant decrease in International Normalised 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 (Alchemy) (125 mg/80 mg) with each chemotherapy cycle or following administration of a single 40 mg dose of Aprepitant (Alchemy) for the prevention of postoperative nausea and vomiting (PONV) (see Section 4.5).

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 (Alchemy) and for one month following the last dose of Aprepitant (Alchemy) (see Section 4.5).

Paediatric Use

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

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.

4.5 Interaction with other medicines and other forms of interaction

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

As a weak (40 mg) to moderate (125 mg/80 mg) inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally co-administered medicinal products that are metabolised through CYP3A4. Aprepitant can increase plasma concentrations of intravenously co-administered medicinal products metabolised through CYP3A4 to a lesser extent.

Aprepitant (Alchemy) should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see Section 4.3).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolised through CYP2C9. Co-administration of Aprepitant (Alchemy) with these medicines or other medicines that are known to be metabolised by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these medicines.

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

5-HT_3 antagonists

In clinical medicine interaction studies, aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg on Days 2 and 3, 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 (Alchemy) (125 mg/80 mg regimen), to achieve exposures of dexamethasone similar to those obtained when it is given without Aprepitant (Alchemy). 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 Section 4.2).

A single dose of aprepitant (40 mg), when co-administered 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 1.3- 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 (Alchemy) (125 mg/80 mg regimen), to achieve exposures of methylprednisolone similar to those obtained when it is given without Aprepitant (Alchemy). 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

In clinical studies, aprepitant (125 mg/80 mg regimen) was administered with the following chemotherapeutic agents metabolised 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 medicine interactions. Caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolised primarily by CYP 3A4. Post-marketing events of neurotoxicity, a potential adverse event of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see Section 4.4).

Docetaxel: In a separate pharmacokinetic study, aprepitant (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a separate pharmacokinetic study, aprepitant (125 mg/80 mg regimen) 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 stabilised 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 Normalised 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 (125 mg/80 mg) with each chemotherapy cycle, or following administration of a single 40 mg dose of aprepitant for the prevention of PONV.

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.

Aprepitant, when given as a 40-mg single oral dose on Day 1, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 8% on Day 2, 16% on Day 4, 15% on Day 8, and 10% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of aprepitant 40 mg and on Days 2, 4, 8, and 15. This effect was not considered clinically important.

Oral contraceptives

Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 μg 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.

In another study, a single dose of an oral contraceptive containing ethinyl estradiol and norgestimate (which is converted to norelgestromin) was administered on Days 1 through 21, and aprepitant 40 mg was given on Day 8. In the study, the AUC of ethinyl estradiol decreased by 4% and 29% on Day 8 and Day 12, respectively, while the AUC of norelgestromin increased by 18% on Day 8 and decreased by 10% on Day 12. In addition, the trough concentrations of ethinyl estradiol and norelgestromin on Days 8 through 21 were generally lower following co-administration of the oral contraceptive with aprepitant 40 mg on Day 8 compared to the trough levels following administration of the oral contraceptive alone.

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

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 metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co- administering these agents with Aprepitant (Alchemy) (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 co-administered 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. This effect was not considered clinically important.

EFFECTS OF OTHER AGENTS ON THE PHARMACOKINETICS OF APREPITANT

Aprepitant is a substrate for CYP3A4; therefore, co-administration of Aprepitant (Alchemy) with medicines that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of Aprepitant (Alchemy) with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached cautiously; but concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

Aprepitant is a substrate for CYP3A4; therefore, co-administration of Aprepitant (Alchemy) with medicines that strongly induce CYP3A4 activity (e.g., rifampicin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of Aprepitant (Alchemy).

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 (Alchemy) with strong CYP3A4 inhibitors should be approached cautiously.

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 approximately 11-fold and the mean terminal half-life decreased approximately 3-fold. Co- administration of Aprepitant (Alchemy) with medicines that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of Aprepitant (Alchemy).

ADDITIONAL INTERACTIONS

Diltiazem

In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of a 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 a 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 Fertility, pregnancy and lactation

Effects on Fertility

Reproductive studies have been performed in rats and rabbits at doses up to 1.5 times the systemic exposure at the adult human dose following oral aprepitant 125 mg 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 medicine should be used during pregnancy only if clearly needed.

Use in Pregnancy

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

Use in Lactation

Aprepitant is excreted in the milk of lactating rats. It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk and because of the possible adverse effects of Aprepitant (Alchemy) on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

No studies of the effects of aprepitant on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with aprepitant may affect some patients' ability to drive or operate machinery. Individual responses to aprepitant may vary (See Section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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. The 3-day oral aprepitant regimen 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, medicine-related clinical adverse experiences were reported in approximately 19% of patients treated with the 3-day oral aprepitant regimen compared with approximately 14% of patients treated with standard therapy. Treatment was discontinued due to medicine- related clinical adverse experiences in 0.6% of patients treated with the 3-day oral aprepitant regimen compared with 0.4% of patients treated with standard therapy.

The most common medicine-related adverse experiences reported in patients treated with the 3-day oral 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 the 3-day oral aprepitant regimen and HEC, the adverse experience profile was generally similar to that seen in the other HEC studies with the 3-day oral aprepitant regimen.

Moderately Emetogenic Chemotherapy (MEC)

In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), 868 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, the 3-day oral aprepitant regimen 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, medicine-related adverse experiences were reported in approximately 14% of patients treated with the 3-day oral aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to medicine-related adverse experiences in 0.7% of patients treated with the 3-day oral aprepitant regimen compared with 0.2% of patients treated with standard therapy.

The most common medicine-related adverse experience reported at a greater incidence in patients treated with the 3-day oral aprepitant regimen than with standard therapy was fatigue (1.4%).

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

In well-controlled clinical studies in patients receiving general balanced anaesthesia, 564 patients were administered 40 mg aprepitant orally and 538 patients were administered 4 mg ondansetron IV. Aprepitant was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

Medicine-related clinical adverse experiences were reported in approximately 4% of patients treated with 40 mg aprepitant compared with approximately 6% of patients treated with 4 mg ondansetron IV.

The most common medicine-related adverse experience reported in patients treated with aprepitant and at a greater incidence than ondansetron was ALT increased (1.1%).

Tabulated list of adverse reactions

Highly and Moderately Emetogenic Chemotherapy

In a pooled analysis of the HEC and MEC studies the following medicine-related adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen and at a greater incidence than standard therapy or in post-marketing use:

[Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), and not known (cannot be estimated from the available data)]*

System organ class	Adverse effect	Frequency
Infection and infestations	candidiasis, staphylococcal infection	rare
Blood and the lymphatic system disorders	anaemia, febrile neutropenia	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	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	uncommon
Respiratory, thoracic and mediastinal disorders	hiccups	common
	oropharyngeal pain, sneezing, cough, post nasal drip, throat irritation	rare

Gastrointestinal disorders	dyspepsia	common
	eructation, nausea, gastroesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence	uncommon
	faeces hard, duodenal ulcer perforation, neutropenic colitis, stomatitis, abdominal distension	rare
Skin and subcutaneous tissue disorders	rash, acne	uncommon
	photosensitivity reactions, hyperhidrosis, seborrhoea, skin lesion, rash pruritic	rare
	pruritus, rash, urticaria, rarely Stevens-Johnson syndrome/toxic epidermal necrolysis	not known*
Musculoskeletal and connective tissue disorders	muscle spasms, muscular weakness	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
	urine output increased, red blood cells urine positive, blood sodium decreased, weight decreased, glucose urine present, neutrophil count decreased	rare

*Reported in post-marketing use.

These 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 medicine.

Prevention of Postoperative Nausea and Vomiting

The following medicine-related adverse experiences were observed in patients treated with aprepitant and at a greater incidence than ondansetron.

[Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1,000)]

System organ class	Adverse effect	Frequency
Psychiatric disorders	insomnia	uncommon
Nervous system disorders	dysarthria, hypoaesthesia, sensory disturbance	uncommon
Eye disorders	miosis, visual acuity reduced	uncommon
Cardiac disorders	bradycardia	uncommon
Respiratory, thoracic and mediastinal disorders	dyspnoea, wheezing	uncommon
Gastrointestinal disorders	abdominal pain upper, bowel sounds abnormal, dry mouth, nausea, stomach discomfort	uncommon
Investigations	ALT increased	common

Description of selected adverse reactions

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.

In addition, two serious adverse experiences were reported in postoperative nausea and vomiting (PONV) clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of subileus.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 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 (Alchemy) should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, medicine-induced emesis may not be effective.

Aprepitant cannot be removed by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, ATC code: A04AD12

Aprepitant is a substance P neurokinin 1 (NK_1) receptor antagonist.

Aprepitant has a unique mode of action; it 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 chemotherapy induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) 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 Pharmacokinetic properties

Absorption

The mean absolute oral bioavailability of aprepitant (125 mg or 80 mg) 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. A separate clinical study in healthy young adults demonstrated that there is no clinically important effect of food on the pharmacokinetics of a single 40 mg dose of aprepitant.

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 μg•hr/mL and 20.1 μg•hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1.5 μg/mL and 1.4 μg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

Following oral administration of a single 40-mg dose of aprepitant in the fasted state, the $AUC_{0-\infty}$ was 7.8 μg•hr/mL, the C_{max}, 0.7 μg/mL, the T_{max}, 3 hours, and the half-life 9 hours.

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 (see Section 5.1).

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 metabolised 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 faeces.

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.

Pharmacokinetics in special populations

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 (Alchemy) 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 (Alchemy) is necessary in elderly patients.

Paediatric

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 (Alchemy) 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 (Alchemy) 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 haemodialysis.

In patients with severe renal insufficiency, the $AUC_{0\text{-}\infty}$ 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 haemodialysis, the $AUC_{0\text{-}\infty}$ 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 medicine was not significantly affected in patients with renal insufficiency compared with healthy subjects. Haemodialysis 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 (Alchemy) is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing haemodialysis.

5.3 Preclinical safety data

Animal Toxicology

Acute Toxicity

The approximate oral LD50 of aprepitant was >2000 mg/kg in female mice and rats. The approximate intraperitoneal LD50 of aprepitant was >800 mg/kg, but <2000 mg/kg in female rats and >2000 mg/kg in female mice.

Chronic Toxicity

The toxicity potential of aprepitant was evaluated in a series of repeated-dose oral toxicity studies in rats and in dogs for up to 1 year.

In rats, oral administration of aprepitant for 6 months at doses up to the maximum feasible dose of 1000 mg/kg twice daily (approximately equivalent to [females] or lower than [males] the adult human dose based on systemic exposure following oral aprepitant 125 mg) produced increased hepatic weights that correlated with hepatocellular hypertrophy, increased thyroidal weights that correlated with thyroid follicular cell hypertrophy and/or hyperplasia, and pituitary cell vacuolation. These findings are a species-specific consequence of hepatic CYP enzyme induction in the rat, and are consistent with changes observed in rats with other structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic CYP enzymes.

In dogs administered aprepitant orally for 9 months at doses ≥5 mg/kg twice daily (greater than or equal to 13 times the adult human dose based on systemic exposure following oral aprepitant 125 mg), toxicity was characterised by slight increases in serum alkaline phosphatase activity and decreases in the albumin/globulin ratio. Significantly decreased body weight gain, testicular degeneration, and prostatic atrophy were observed at doses ≥25 mg/kg twice daily (greater than or equal to 31 times the adult human dose based on systemic exposure following oral aprepitant 125 mg). A slight increase in hepatic weights with no histologic correlate was seen at 500 mg/kg twice daily (70 times the adult human dose based on systemic exposure following oral aprepitant 125 mg). No toxicity was observed in dogs administered 32 mg/kg/day (6 times the adult human dose based on systemic exposure following oral aprepitant 125 mg) for 1 year.

Carcinogenesis

Carcinogenicity studies were conducted in mice and rats for 2 years with oral aprepitant. Mice developed hepatocellular adenomas and/or carcinomas at doses of 500 to 2000 mg/kg/day (females) and hepatocellular carcinomas at doses of 1000 and 2000 mg/kg/day (males). Systemic exposures at these doses in mice were approximately 2.5 to 3.6 times the exposure in humans at the recommended dose. Rats developed hepatocellular adenomas at doses of 5 to 1000 mg/kg twice daily (females) and 125 mg/kg twice daily (males), hepatocellular carcinomas at doses of 125 to 1000 mg/kg twice daily (females), thyroid follicular cell adenomas at doses of 125 to 1000 mg/kg twice daily (females and males), and thyroid follicular cell carcinomas at doses of 125 to 1000 mg/kg twice daily (males). Systemic exposures at these doses in rats were lower than or up to approximately 2 times the exposure in humans at the recommended dose. Liver and thyroid tumours of these types are a species-specific consequence of hepatic CYP enzyme induction in rodents, and are consistent with changes observed in rodents with other structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic CYP enzymes.

Mutagenesis

Aprepitant was neither mutagenic nor genotoxic in assays conducted to detect mutagenicity, DNA strand breaks, and chromosomal aberrations. Aprepitant was negative in the in vitro microbial and TK6 human lymphoblastoid cell mutagenesis assays, the in vitro alkaline elution/rat hepatocyte DNA strand break test, the in vitro chromosomal aberration assay in Chinese hamster ovary cells, and the in vivo mouse micronucleus assay in bone marrow.

Reproduction

Aprepitant administered to female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (approximately equivalent to the adult human dose based on systemic exposure following oral aprepitant 125 mg) had no effects on mating performance, fertility, or embryonic/foetal survival.

Administration of aprepitant to male rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (lower than the adult human dose based on systemic exposure following oral aprepitant 125 mg) produced no effects on mating performance, fertility, embryonic/foetal survival, sperm count and motility, testicular weights, or the microscopic appearance of the testes and epididymides.

Development

In rats and rabbits administered oral doses of aprepitant up to 1000 mg/kg twice daily and 25 mg/kg/day, respectively (up to 1.5 times the systemic exposure at the adult human dose following oral aprepitant 125 mg), there was no evidence of developmental toxicity as assessed by embryonic/foetal survival, foetal body weight, and foetal external, visceral, and skeletal morphology. Placental transfer of aprepitant occurred in rats and rabbits at these doses. Concentrations of aprepitant in foetal plasma were approximately 27% and 56% of maternal plasma concentrations in rats and rabbits, respectively.

Significant concentrations of aprepitant were observed in the milk of lactating rats administered 1000 mg/kg twice daily. At this dose, the mean milk Medicine concentration was 90% of the mean maternal plasma concentration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule of Aprepitant (Alchemy) contains the following inactive ingredients:
- Hypromellose (2910)
- Poloxamer 407
- Sucrose
- Microcrystalline cellulose (spheres)

The capsule shell excipients are:
- Gelatin
- Sodium laurilsulfate
- Titanium dioxide (E171, CI 77891)
- Black printing ink containing shellac, iron oxide black (E172) and propylene glycol (E1520)

The 40 mg capsule shell also contains:
- Iron oxide yellow (E172, CI 77492)

The 125 mg capsule shell also contains:
- Iron oxide red (E172, CI77491)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 30°C in its original packaging to protect from moisture.

6.5 Nature and contents of container

The 80 mg capsule and the 125 mg capsule come in a single pack containing one 125 mg capsule and two 80 mg capsules. ***(Not available in NZ)***

The 40 mg capsule come in a pack containing one or five 40 mg capsule(s). ***(Not available in NZ)***

The 80 mg capsule come in a pack containing one or two 80 mg capsules. ***(The two capsule pack is not available in NZ)***

The 125 mg capsule come in a pack containing five 125 mg capsules. ***(Not available in NZ)***

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Alchemy Health Limited
120 Ngapuhi Road
Remuera
Auckland 1050
NEW ZEALAND

Medical enquiries: 0508 ALCHEMY (0508 252436)

9 DATE OF FIRST APPROVAL

18 August 2022

10 DATE OF REVISION OF THE TEXT

23 October 2024

Summary Table of Changes

Section changed	Summary of new information
All	Changed trade name to include '(Alchemy)'. Added section hyperlinks.
1	Indicated that only the 80 mg strength is available.
6.3	Shelf life extended from 30 months to 4 years.
6.5	Added one capsule pack for 80 mg strength. Indicated packs that were not available in NZ.