AUSTRALIAN PRODUCT INFORMATION – APREPITANT APOTEX Capsules (aprepitant)

1 NAME OF THE MEDICINE

Aprepitant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aprepitant is a substance P neurokinin 1 (NK1) receptor antagonist.

Aprepitant is a white to off-white crystalline solid. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

Each capsule of APREPITANT APOTEX for oral administration contains 40 mg, 80 mg, 125 mg or 165 mg of aprepitant.

Excipient with known effect:

Each 40 mg capsule contains 40 mg of sucrose.
Each 80 mg capsule contains 80 mg of sucrose.
Each 125 mg capsule contains 125 mg of sucrose.
Each 165 mg capsule contains 165 mg of sucrose.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

APREPITANT APOTEX is available in a 165 mg, 125 mg, 80 mg and 40 mg capsule.

The 165 mg capsules are presented as opaque hard gelatin capsules with a blue cap and white body, printed with “165mg” on the body.

The 125 mg capsules are presented as opaque hard gelatin capsules with a pink cap and white body, printed with “125mg” on the body.

The 80 mg capsules are presented as opaque hard gelatin capsules with a white cap and white body, printed with “80mg” on the body.

The 40 mg capsules are presented as opaque hard gelatin capsules with a yellow cap and white body, printed with “40mg” on the body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.
- moderately emetogenic cancer chemotherapy

Aprepitant 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 is given for 1 day or 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist.

1-Day Regimen of aprepitant:

The recommended dose of aprepitant for the 1-day oral regimen is 165 mg orally 1 hour prior to chemotherapy treatment on Day 1 only.

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

	Day 1	**Day 2**	**Day 3**	**Day 4**
Aprepitant	165 mg orally	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
Ondansetron	See package insert for ondansetron 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. Dexamethasone should also be administered in the evenings on Days 3 and 4. The dose of dexamethasone accounts for drug interactions.				

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

	Day 1 only
Aprepitant	165 mg orally
Dexamethasone**	12 mg orally
Ondansetron	See package insert for ondansetron for appropriate dosing information
** Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.	

3-Day Regimen of aprepitant:

The recommended dose of aprepitant 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	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron	See package insert for ondansetron 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 accounts for drug interactions.				

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

	Day 1	Day 2	Day 3
Aprepitant	125 mg orally	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
Ondansetron	See package insert for ondansetron for appropriate dosing information	none	none
** Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.			

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

The recommended oral dosage of aprepitant is 40 mg within 3 hours prior to induction of anaesthesia.

General Information

See **section 4.5 Interactions with other medicines and other forms of interactions** for additional information on the administration of aprepitant with corticosteroids.

Refer to the full Product Information for coadministered antiemetic agents.

Aprepitant may be taken with or without food. It is recommended that aprepitant 165 mg be taken with or without a light (low fat) meal, as administration with a high fat meal results in a 47% increase in systemic exposure of aprepitant (see **section 5.2 Pharmacokinetic properties**).

No dosage adjustment is necessary based on age, gender or race.

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).

4.3 CONTRAINDICATIONS

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

Aprepitant 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 drugs, potentially causing serious or life- threatening reactions.

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 Interactions with other medicines and other forms of interactions**). Moderate inhibition of CYP3A4, by aprepitant (125 mg/80 mg 3-day oral regimen or 165 mg single dose) could result in elevated plasma concentrations of these concomitant medicinal products (see section **4.5 Interactions with other medicines and other forms of interactions**). 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 Interactions with other medicines and other forms of interactions**).

Coadministration 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 (125 mg/80 mg) or administration of a single 165 mg dose of aprepitant with each chemotherapy cycle or following administration of a single 40 mg dose of aprepitant for the prevention of postoperative nausea and vomiting (PONV) (see section **4.5 Interactions with other medicines and other forms of interactions**).

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 and for one month following the last dose of aprepitant (*see* section **4.5 Interactions with other medicines and other forms of interactions**).

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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

General

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor and inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment, the single 40 mg dose of aprepitant recommended for PONV results in a weak inhibition of CYP3A4. Aprepitant has been studied at higher doses. During treatment for chemotherapy induced nausea and vomiting (CINV), the 3-day 125 mg/80 mg regimen of aprepitant is a moderate inhibitor of CYP3A4. After the end of treatment with the 3-day CINV regimen, aprepitant causes a transient moderate induction of CYP2C9 and a transient mild induction of CYP3A4 and glucuronidation. The effects of induction by a single 40 mg dose of aprepitant have not been studied, but it is unlikely that a 40 mg single dose will cause any clinically relevant induction.

Effect of aprepitant on the pharmacokinetics of other agents

As a weak (40 mg) to moderate (125 mg/80 mg, 165 mg) inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally coadministered medicinal products that are metabolised through CYP3A4. Aprepitant can increase plasma concentrations of intravenously coadministered medicinal products metabolised through CYP3A4 to a lesser extent.

Caution should be exercised in using aprepitant concurrently with drugs which have a narrow therapeutic index and are known to be metabolised primarily by CYP3A4, such as cyclosporine, sirolimus and tacrolimus.

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

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

5-HT3 antagonists:

In clinical drug interaction studies, aprepitant 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 coadministered orally as 20 mg on Day 1, and aprepitant when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate by 2.2-fold, on Days 1 and 5. The usual oral dexamethasone doses should be reduced by approximately 50% when coadministered with aprepitant (125 mg/80 mg regimen) to achieve exposures of dexamethasone similar to those obtained when it is given without aprepitant. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting studies with aprepitant reflects an approximate 50% reduction of the dose of dexamethasone (see **section 4.2 Dose and method of administration**).

Aprepitant, when given as a single dose of 200 mg in the fed state (standard light breakfast) on Day 1 with oral dexamethasone coadministered orally as 12 mg on Day 1 and 8 mg on Days 2 through 4, increased the AUC of dexamethasone by 2.1- and 2.3-fold on Days 1 and 2, to a lesser extent (1.4-fold increase) on Day 3, and had no effect on Day 4 (1.1-fold increase). The daily dose of dexamethasone on Days 1 and 2 should be reduced by approximately 50% when coadministered with aprepitant 165 mg on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without aprepitant 165 mg.

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 coadministered 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 coadministered with aprepitant (125 mg/80 mg regimen), to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant.

Chemotherapeutic agents:

Chemotherapy agents that are known to be metabolised by the CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, aprepitant (125 mg/80 mg regimen) was administered commonly with etoposide, vinorelbine, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. Adequate data are not available on interactions between aprepitant and other chemotherapy agents primarily metabolised by CYP3A4.Particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolised primarily by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see **section 4.4 Special warnings and precautions for use**).

Docetaxel: In an interaction 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.

Formal interaction studies have not been conducted with other chemotherapy agents.

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) or administration of a single 165 mg dose of aprepitant with each chemotherapy cycle, or following administration of a single 40 mg dose of aprepitant for the prevention of PONV.

Oral contraceptives:

Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%.

In another study, a 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.

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 and for one month following the last dose of aprepitant.

Tolbutamide:

aprepitant, when given as 125mg on Day 1 and 80mg/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 500mg was administered orally prior to the administration of the 3-day regimen of aprepitant and on Days 4, 8 and 15.

Midazolam:

Aprepitant increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 through 5. A single dose of aprepitant 200 mg in the fed state (standard light breakfast) coadministered orally with 2 mg midazolam increased the AUC of midazolam by 3.2-fold on Day 1. No clinically important effect resulted on Day 4 (midazolam AUC 1.2-fold increase) and a slight change in midazolam AUC was observed on Day 8 (35% decrease). The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with aprepitant (125 mg/80 mg or 165 mg).

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.

Effect of other agents on the pharmacokinetics of aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of aprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) 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, coadministration of aprepitant with drugs that strongly induce CYP3A4 activity (e.g. rifampicin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant.

Concomitant administration of aprepitant with St. John's wort 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. Concomitant administration of aprepitant 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. Coadministration of aprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of aprepitant.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Additional interactions

Diltiazem: In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate, or blood pressure beyond those changes induced by diltiazem alone.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Aprepitant administered to male or female rats at doses up to 1000 mg/kg twice daily (approximately 1.5 times the adult human dose based on systemic exposure following oral aprepitant 125 mg in females, or lower than the adult human dose in males) had no effects on mating performance, fertility, or embryonic/foetal survival. Sperm count and motility were unaffected in males.

Use in pregnancy

(Category B1)

Reproductive studies performed in rats and rabbits at doses up to about 1.5 times the systemic exposure at the adult human dose following oral aprepitant 125 mg have revealed no evidence of harm to the foetus 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.

Use in lactation

Significant concentrations of aprepitant were observed in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of aprepitant on nursing infants, 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The overall safety of aprepitant was evaluated in approximately 6500 individuals.

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 544 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy, 868 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into the Multiple-Cycle extensions for up to 4 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.

Highly Emetogenic Chemotherapy (HEC)

In Cycle 1, in patients receiving HEC, drug-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 drug-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. **Table 1** shows the drug- related adverse experiences reported at an incidence ≥0.5% (and at a greater incidence than standard therapy) in patients treated with the 3-day oral aprepitant regimen.

Table 1: Drug-Related Adverse Experiences (Incidence ≥ 0.5% and Greater Than Standard Therapy) Occurring in Patients Receiving HEC Who Were Treated With the 3-Day Oral Aprepitant Regimen for CINV in Clinical Studies

	Aprepitant Regimen* (N=544)	**Standard Therapy**** (N=550)
Blood and Lymphatic System Disorders		
Anaemia	0.6	0.0
Metabolism and Nutrition Disorders		
Decreased appetite	2.0	0.5
Nervous System Disorders		
Dizziness	0.9	0.7
Headache	2.0	1.8

	Aprepitant Regimen* (N=544)	Standard Therapy** (N=550)
Respiratory, Thoracic and Mediastinal Disorders		
Hiccups	4.6	2.9
Gastrointestinal Disorders		
Abdominal Pain	0.9	0.5
Constipation	2.4	2.0
Diarrhoea	1.1	0.9
Dyspepsia	2.6	2.0
Gastroesophageal reflux disease	0.7	0.2
Nausea†	0.7	0.0
General Disorders and Administrative Site Conditions		
Asthenia	1.5	0.2
Investigations		
ALT increased	2.8	1.1
AST increased	1.1	0.7
Blood alkaline phosphatase increased	0.7	0.2

*Aprepitant Regimen: aprepitant 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus Ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.

**Standard Therapy: Placebo plus Ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

†These adverse experiences of nausea occurred 2 or 3 days after the last dose of study drug (Study Day 6 or greater; i.e., after the period in which efficacy was assessed)

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 the combined analysis of Cycle 1 data in patients receiving MEC, drug-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 drug-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. **Table 2** shows the drug-related adverse experiences reported at an incidence ≥0.5% and at a greater incidence than standard therapy in patients treated with the 3-day oral aprepitant regimen.

Table 2: Drug-Related Adverse Experiences (Incidence ≥0.5% and Greater Than Standard Therapy) Occurring in Patients Receiving MEC Who Were Treated With the 3-day Oral Aprepitant Regimen for CINV in Clinical Studies

	Aprepitant Regimen* (N=868)	Standard Therapy** (N=846)
Psychiatric Disorders		
Anxiety	0.5	0.0
Nervous System Disorders		
Dizziness	0.7	0.6
Somnolence	0.6	0.2
Respiratory, Thoracic and Mediastinal Disorders		
Hiccups	0.5	0.2
Gastrointestinal Disorders		
Dyspepsia	0.8	0.4
Eructation	1.0	0.1

	Aprepitant Regimen* (N=868)	Standard Therapy** (N=846)
General Disorders and Administration Site Conditions		
Fatigue	1.4	0.9

*Aprepitant Regimen: aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

Highly and Moderately Emetogenic Chemotherapy

In a pooled analysis of the HEC and MEC studies, the following drug-related adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen at a greater incidence than standard therapy and not described above:

Blood and lymphatic system disorders: febrile neutropenia

Infection and infestations: candidiasis, staphylococcal infection.

Metabolism and nutrition disorders: polydipsia.

Psychiatric disorders: disorientation, euphoric mood.

Nervous system disorders: cognitive disorder, lethargy, dysgeusia.

Eye disorders: conjunctivitis.

Ear and labyrinth disorders: tinnitus.

Cardiac disorders: cardiovascular disorder, bradycardia, palpitations.

Vascular disorders: hot flush

Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain, postnasal drip, sneezing, throat irritation.

Gastrointestinal disorders: abdominal distension, dry mouth, faeces hard, flatulence, neutropenic colitis, duodenal ulcer perforation, stomatitis, vomiting.

Skin and subcutaneous tissue disorders: acne, hyperhidrosis, seborrhoea, photosensitivity reaction, rash pruritic, rash, skin lesion.

Musculoskeletal and connective tissue disorders: muscular weakness, muscle spasms.

Renal and urinary disorders: dysuria, pollakiuria.

General disorders and administration site conditions: chest discomfort, oedema, gait disturbance, malaise.

Investigations: blood sodium decreased, red blood cells urine positive, neutrophil count decreased, weight decreased, glucose urine present, urine output increased.

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 other clinical studies, isolated cases of serious adverse experiences were reported. In another chemotherapy induced nausea and vomiting (CINV) study, Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy. Angioedema and urticaria were reported in a patient receiving aprepitant in a non- CINV study.

Oral administration of a single 165 mg dose of aprepitant was generally well tolerated in healthy adults.

Based on a comparable pharmacokinetic/pharmacodynamic profile, the 1-day oral regimen of aprepitant 165 mg administered in the fasted state or with a light (low fat) meal is anticipated to have a similar safety and tolerability profile to that of the 1-day regimen of fosaprepitant

150 mg, an IV prodrug of aprepitant (available in another brand), and the 3-day oral aprepitant regimen in chemotherapy patients (see **section 5.1 Pharmacodynamic properties**).

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

In well-controlled clinical studies in patients receiving general 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.

Clinical adverse experiences were reported in approximately 60% of patients treated with 40 mg aprepitant compared with approximately 64% of patients treated with 4 mg ondansetron IV. **Table 3** shows the percent of patients with clinical adverse experiences reported at an incidence ≥3% of the combined studies.

Table 3: Percent of Patients Receiving General Anesthesia With Clinical Adverse Experiences (Incidence ≥3%)

	Aprepitant 40 mg (N=564)	**Ondansetron** (N=538)
Infections and Infestations		
Urinary Tract Infection	2.3	3.2
Blood and Lymphatic System Disorders		
Anaemia	3.0	4.3
Psychiatric Disorders		
Insomnia	2.1	3.3
Nervous System Disorders		
Headache	5.0	6.5
Cardiac Disorders		
Bradycardia	4.4	3.9
Vascular Disorders		
Hypertension	2.1	3.2
Hypotension	5.7	4.6
Gastrointestinal Disorder		
Constipation	8.5	7.6
Flatulence	4.1	5.8
Nausea	8.5	8.6
Vomiting	2.5	3.9
Skin and Subcutaneous Tissue Disorders		
Pruritus	7.6	8.4
General Disorders and General Administration Site Conditions		
Pyrexia	5.9	10.6

The following additional clinical adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant:

Infections and infestations: postoperative infection

Metabolism and nutrition disorders: hypokalaemia, hypovolaemia.

Nervous system disorders: dizziness, hypoaesthesia, syncope.

Vascular disorders: haematoma

Respiratory, thoracic and mediastinal disorders: dyspnoea, hypoxia, respiratory depression.

Gastrointestinal disorders: abdominal pain, abdominal pain upper, dry mouth, dyspepsia.

Skin and subcutaneous tissue disorders: urticaria

General disorders and administrative site conditions: hypothermia, pain.

Investigations: blood pressure decreased

Injury, poisoning and procedural complications: operative haemorrhage, wound dehiscence.

Other adverse experiences (incidence ≤0.5%) reported in patients treated with aprepitant 40 mg for PONV included:

Nervous system disorders: dysarthria, sensory disturbance.

Eye disorders: miosis, visual acuity reduced.

Respiratory, thoracic and mediastinal disorders: wheezing

Gastrointestinal disorders: bowel sounds abnormal, stomach discomfort.

In addition, two serious drug-related adverse experiences were reported in PONV clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of subileus.

Laboratory Adverse Experiences

One laboratory adverse experience, haemoglobin decreased (40 mg aprepitant 3.8%, ondansetron 4.2%), was reported at an incidence ≥3% in a patient receiving general anaesthesia.

The following additional laboratory adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant 40 mg: blood albumin decreased, blood bilirubin increased, blood glucose increased, blood potassium decreased, glucose urine present.

The adverse experience of ALT increased occurred with similar incidence in patients treated with aprepitant 40 mg (1.1%) as in patients treated with ondansetron 4 mg (1.0%).

Other Studies

Angioedema and urticaria were reported as serious adverse experiences in a patient receiving aprepitant in a non-CINV/non-PONV study.

Post Marketing Experience:

The following 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 drug.

Skin and subcutaneous tissue disorders*:* pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis

Immune system disorders: hypersensitivity reactions including anaphylactic reactions.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at **http://www.tga.gov.au/reporting-problems** or contact Apotex Medical Information enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

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 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 haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant.

Fosaprepitant IV formulation is unavailable in this brand, however is available in another brand. Pharmacodynamic and pharmacokinetic information obtained using Fosaprepitant IV formulations are also included in the following sub-sections for prescriber information.

Cardiac Electrophysiology

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

Brain NK1 Receptor Occupancy Assessed by Positron Emission Tomography

A positron emission tomography study in healthy young men administered a single oral dose of 165 mg aprepitant or a single intravenous dose of 150 mg fosaprepitant demonstrated similar brain NK_1 receptor occupancy at $T_{max,}$ (≥ 99 %), 24 hours (≥ 99 %), 48 hours (≥ 97 %), and 120 hours (37 to 76 %) following dosing. Following administration of a single oral dose of 165 mg aprepitant or a single intravenous dose of 150 mg fosaprepitant, T_{max} was approximately 4 hours or 30 minutes post dose, respectively. Occupancy of brain NK_1 receptors by aprepitant correlate well with aprepitant plasma concentrations.

Mechanism of action

Aprepitant is a selective high affinity antagonist at human substance-P neurokinin-1 (NK1) receptors. Aprepitant showed at least 3,000-fold selectivity for the NK1 receptor over other enzyme, transporter, ion-channel and receptor sites, including the dopamine and serotonin (5HT3) receptors that are targets for existing chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) therapies. Aprepitant has been shown in animal models 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 $5HT_3$-receptor antagonist ondansetron, and the corticosteroid dexamethasone against cisplatin-induced emesis.

Clinical trials

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

3-Day Regimen of aprepitant

Oral administration of aprepitant in combination with ondansetron and dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic chemotherapy (HEC and MEC) in well-controlled clinical studies.

Highly Emetogenic Chemotherapy (HEC)

In 2 multicentre, randomised, parallel, double-blind, controlled clinical studies, the aprepitant regimen was compared with standard therapy in 1094 patients receiving a chemotherapy

regimen that included cisplatin ≥70 mg/m^2. Some patients also received additional chemotherapeutic agents such as gemcitabine, etoposide, fluorouracil, vinorelbine tartrate, doxorubicin, cyclophosphamide, paclitaxel, or docetaxel. The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg once daily on Days 2 through 4. Standard therapy consisted of placebo in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg on Day 1 and 8 mg twice daily on Days 2 through 4. Although a 32mg IV dose of ondansetron was used in clinical trials, this may no longer be the currently recommended dose. See the package insert for ondansetron for appropriate dosing information.

The antiemetic activity of aprepitant was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no significant nausea (maximum VAS <25 mm).

A summary of the key study results from each individual study analysis is shown in **Table 4** and in **Table 5**.

Table 4: Percent of Patients Responding by Treatment Group and Phase for Study 1 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N=260)[†] %	Standard Therapy (N=261)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[‖]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	0.005
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	>0.050
Delayed phase	51	48	>0.050
No Significant Nausea			
Overall	73	66	>0.050
Delayed phase	75	69	>0.050

[†]N: Number of patients (older than18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

‡Overall: 0 to 120 hours post-cisplatin treatment.

§Acute phase: 0 to24 hours post-cisplatin treatment.

||Delayed phase: 25 to 120 hours post-cisplatin treatment.

Visual analogue scale (VAS) score range: 0 mm=no nausea; 100 mm=nausea as bad as it could be.

Table 4 includes nominal p-values not adjusted for multiplicity.

Table 5: Percent of Patients Responding by Treatment Group and Phase for Study 2 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N=261)† %	Standard Therapy (N=263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase||	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	0.021
Delayed phase	53	40	0.004
No Significant Nausea			
Overall	71	64	>0.050
Delayed phase	73	65	>0.050

†N: Number of patients (older than18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

‡Overall: 0 to 120 hours post-cisplatin treatment.

§Acute phase: 0 to24 hours post-cisplatin treatment.

||Delayed phase: 25 to 120 hours post-cisplatin treatment.

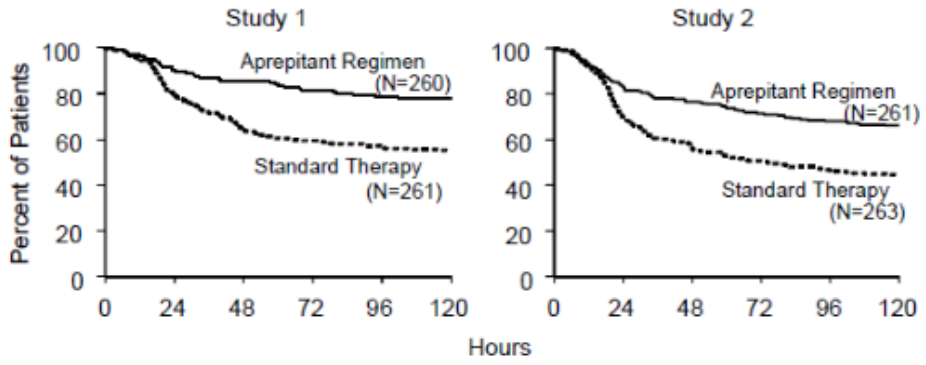
Visual analogue scale (VAS) score range: 0 mm=no nausea; 100 mm=nausea as bad as it could be.

Table 5 includes nominal p-values not adjusted for multiplicity.

In both studies, a statistically significant, higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favour of the aprepitant regimen was also observed when the acute phase and the delayed phase were analysed separately.

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in **Figure 1**.

Figure 1: Percent of Patients Who Remain Emesis Free Over Time - Cycle 1

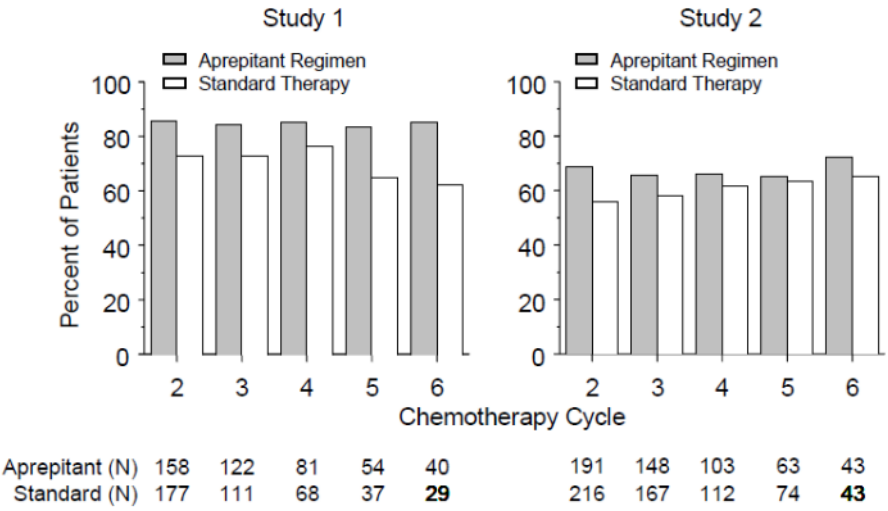


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity

Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase III studies using the Functional Living Index–Emesis (FLIE), a validated nausea- and vomiting-specific patient-reported outcome measure. Minimal or no impact of nausea and vomiting on patients' daily lives is defined as a FLIE total score >108. In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

Multiple-Cycle Extension: In the same 2 clinical studies, patients continued into the Multiple Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with no emesis and no significant nausea by treatment group at each cycle is depicted in **Figure 2**. Antiemetic effectiveness for the patients receiving the aprepitant regimen is maintained throughout the repeat cycles for those patients continuing in each of the multiple cycles.

Figure 2: Proportion of Patients with No Emesis and No Significant Nausea By Treatment Group and Cycle



Moderately Emetogenic Chemotherapy (MEC)

In a multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 866 breast cancer patients receiving a chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2). Some patients also received other chemotherapeutic agents such as fluorouracil, methotrexate, docetaxel or paclitaxel. The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1. Refer to the table below:

Treatment Regimen	Day 1	Days 2 and 3
Aprepitant	Aprepitant 125mg Ondansetron 16mg (2x8mg) Dexamethasone 12mg	Aprepitant 80mg Ondansetron placebo (every 12 hours)
Standard	Aprepitant placebo Ondansetron 16 mg (2x8mg) Dexamethasone 20mg	Aprepitant placebo daily Ondansetron 8mg daily (every 12 hours)

The antiemetic activity of aprepitant was evaluated during the acute phase (0 to 24 hours post-chemotherapy treatment), the delayed phase (25 to 120 hours post-chemotherapy treatment) and overall (0 to 120 hours post-chemotherapy treatment) in Cycle 1. Efficacy was based on evaluation of the following composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no rescue therapy.

A summary of the key study results is shown in **Table 6**.

Table 6: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

	Aprepitant Regimen* (N=433)† %	Standard Therapy** (N=424)† %	p-Value
COMPOSITE MEASURES			
Complete Response (no emesis and no rescue therapy)			
Overall+	51	42	0.015
Acute phase§	76	69	0.034
Delayed phase‖	55	49	0.064
No Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108)			
Overall	64	56	0.019
INDIVIDUAL MEASURES			
No Emesis			
Overall	76	59	<0.001
Acute phase	88	77	<0.001
Delayed phase	81	69	<0.001
No Rescue Therapy			
Overall	59	56	0.480
Acute phase	83	80	0.366
Delayed phase	63	60	0.407
No Significant Nausea			
Overall	61	56	0.116
Acute phase	80	78	0.699
Delayed phase	65	62	0.219

*Aprepitant Regimen: aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.

**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

†N: Number of patients included in the primary analysis of complete response.

‡Overall: 0 to 120 hours post-chemotherapy treatment.

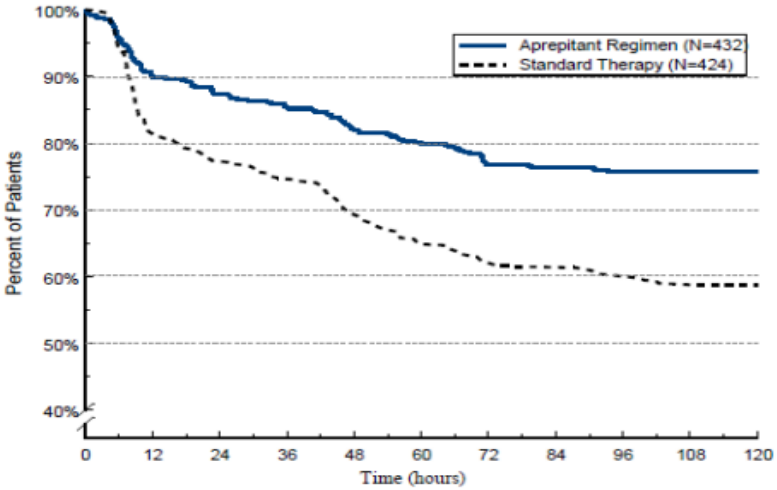
§Acute phase: 0 to 24 hours post-chemotherapy treatment.

‖Delayed phase: 25 to 120 hours post-chemotherapy treatment.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen (51%) in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy (42%). The unadjusted absolute difference in complete response (8.3%) represents a 20% relative improvement (relative risk ratio = 1.2, aprepitant regimen over standard therapy).

In this study, the estimated time to first emesis after initiation of chemotherapy treatment was significantly (p<0.001) longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with the standard therapy group as depicted in **Figure 3**.

Figure 3: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1



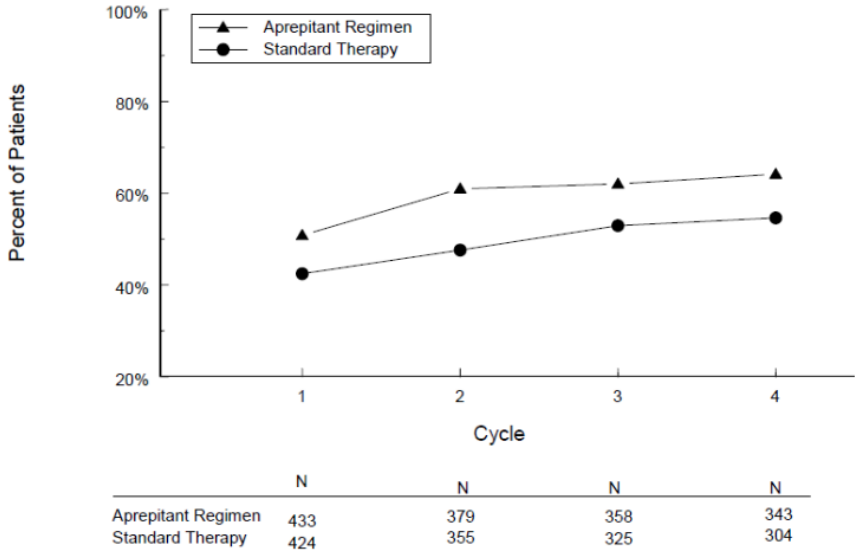
Aprepitant Regimen: aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.

Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.

Multiple-Cycle Extension: A total of 744 patients receiving MEC continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles. The response rates are depicted in **Figure 4**.

Figure 4: Percent of Patients Receiving Moderately Emetogenic Chemotherapy With No Emesis and No Rescue Therapy by Treatment Group and Cycle



Aprepitant Regimen: aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.

Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

In a second multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 patients receiving a chemotherapy regimen that included any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide IV (<1500 mg/m^2); or cytarabine IV (>1 g/m^2). Patients who were randomised to receive the aprepitant regimen consisted of 76% women and 24% men. Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumour types including 52% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynaecological cancers. The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

The antiemetic activity of aprepitant was evaluated during the overall phase (0 to 120 hours post- chemotherapy treatment) in Cycle 1. Efficacy was based on the evaluation of the following endpoints:

Primary endpoint:

- no vomiting in the overall period (0 to 120 hours post-chemotherapy)

Other pre-specified endpoints:

- complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy)
- time to first vomiting episode overall (0 to 120 hours post-chemotherapy)
- no vomiting – Acute (0 to 24 hours following initiation of chemotherapy infusion) and Delayed (25 to 120 hours following initiation of chemotherapy infusion)
- complete response - Acute and Delayed, as defined above
- no use of rescue therapy – Overall, Acute, and Delayed, as defined above
- no Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108) – Overall, as defined above
- no vomiting and no significant nausea (VAS <25 mm) – Overall, as defined above

A summary of the key study results is shown in **Table 7**.

Table 7: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 – Cycle 1

ENDPOINTS	Aprepitant Regimen* (N=430)† %	Standard Therapy** (N=418)† %	p-Value‡
PRIMARY ENDPOINT			
No Vomiting			
Overall§	76	62	<0.0001
KEY SECONDARY ENDPOINT			
Complete Response¶			
Overall§	69	56	0.0003
OTHER SECONDARY ENDPOINTS			
No Vomiting			
Acute phase#	92	84	0.0002
Delayed phaseÞ	78	67	0.0005
No Impact on Daily Life (FLIE total score >108)			
Overall	73	66	0.035
Complete Response			
Acute phase	89	80	0.0005
Delayed phase	71	61	0.0042
No Use of Rescue Therapy			
Overall	81	75	0.0427ß
Acute phase			0.0179ß
Maleà	97	100	
Femaleà	95	88	
Delayed phase	84	79	0.0922ß
No Vomiting and No Significant Nausea (VAS <25 mm)			
Overall	65	53	0.0011

*Aprepitant Regimen: aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.

**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

†N = Number of patients who received chemotherapy treatment, study drug, and had at least one post-treatment efficacy evaluation.

‡Hochberg's procedure was used as a multiplicity adjustment when testing secondary endpoints for significance.

§Overall: 0 to 120 hours post chemotherapy treatment.

¶Complete Response = No Vomiting with no rescue therapy

Acute phase: 0 to 24 hours following initiation of chemotherapy infusion.

Þ Delayed phase: 25 to 120 hours following initiation of chemotherapy infusion.

ßNot statistically significant.

àData are shown separately for males and females per prespecified analytic plan

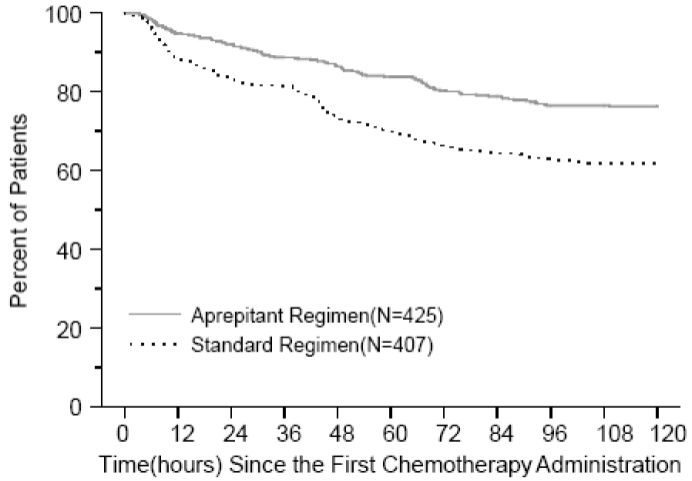
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

In this study, a statistically significantly (p<0.0001) higher proportion of patients receiving the aprepitant regimen (76%) in Cycle 1 had no vomiting (primary endpoint) during the overall phase compared with patients receiving standard therapy (62%). In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response in

the overall phase (0-120 hours), compared with patients receiving standard therapy. Aprepitant was numerically superior versus standard therapy regardless of age, gender, or tumor type (breast, gastrointestinal, lung or other) as assessed by the No Vomiting and Complete Response endpoints.

In this study, the estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen, and the incidence was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in **Figure 5**.

Figure 5: Kaplan-Meier Curves for Time to First Vomiting Episode From Start of Chemotherapy Administration in the Overall Phase – Cycle 1 (Full Analysis Set Patient Population)



In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.

1-Day Regimen of Fosaprepitant

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant. Based on a comparable pharmacokinetic/pharmacodynamic profile, the 1-day oral regimen of aprepitant 165 mg is anticipated to have a similar efficacy profile to that of the 1-day regimen of fosaprepitant 150 mg and 3-day regimen of oral aprepitant (see **section 5 Pharmacological properties**).

In a randomised, parallel, double-blind, active-controlled study, fosaprepitant 150 mg (N=1147) was compared with a 3-day aprepitant regimen (N=1175) in patients receiving a highly emetogenic chemotherapy regimen that included cisplatin (≥70 mg/m^2). Other concomitant chemotherapy agents were administered similar to those in prior HEC studies described above. The fosaprepitant regimen consisted of fosaprepitant 150 mg on Day 1 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1, 8 mg on Day 2, and 8 mg twice daily on Days 3 and 4. The aprepitant regimen consisted of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg daily on Days 2 through 4. Fosaprepitant placebo, aprepitant placebo, and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding. Although a 32mg IV dose of ondansetron was used in the clinical trials, this may no longer be the currently recommended dose. Please see the pack insert for ondansetron for appropriate dosing information.

Efficacy was based on the evaluation of the following composite measures: complete response in both the overall and delayed phases and no vomiting in the overall phase. aprepitant IV 150 mg was shown to be non-inferior to that of the 3-day regimen of aprepitant. A summary of the primary and secondary endpoints is shown in **Table 8**.

Table 8: Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase – Cycle 1

ENDPOINTS*	Fosaprepitant Regimen (N=1106)** %	Aprepitant Regimen (N=1134)** %	Difference† (95% CI)
Complete Response‡			
Overall§	71.9	72.3	-0.4 (-4.1, 3.3)
Delayed phase§§	74.3	74.2	0.1 (-3.5, 3.7)
No Vomiting			
Overall§	72.9	74.6	-1.7 (-5.3, 2.0)

*Primary endpoint is bolded.

**N: Number of patients included in the primary analysis of complete response.

†Difference and confidence interval (CI) were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

‡Complete Response = no vomiting and no use of rescue therapy.

§Overall = 0 to 120 hours post-initiation of cisplatin chemotherapy.

§§Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV)

In two multicentre, randomised, double-blind, active comparator-controlled, parallel-group clinical studies, aprepitant was compared with ondansetron for the prevention of postoperative nausea and vomiting in 1658 adult patients undergoing open abdominal surgery. The majority of patients were women (>90%), mainly undergoing gynaecological surgery. Patients were randomised to receive 40 mg aprepitant, 125 mg aprepitant, or 4 mg ondansetron. Aprepitant was given orally with 50 mL of water 1 to 3 hours before anaesthesia. Ondansetron was given intravenously immediately before induction of anaesthesia.

The antiemetic activity of aprepitant was evaluated during the 0 to 48 hour period following the end of surgery. Efficacy measures included:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- complete response (defined as no emetic episodes and no use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 48 hours following the end of surgery (secondary)
- no use of rescue therapy in the 0 to 24 hours following the end of surgery (exploratory)
- nausea severity (measured on a verbal rating score/VRS) in the 0 to 24 hours following the end of surgery (exploratory)
- time to first emesis in the 0 to 48 hours following the end of surgery (exploratory)

A closed testing procedure was applied to control the type I error for the primary end points.

The results demonstrate that a higher percentage of post-surgical patients will experience complete response (no emesis and no use of rescue) with aprepitant 40 mg than with ondansetron 4 mg (lower bound of C.I. is 0.0 indicating borderline significance) as described in **Table 9**.

Table 9: Percent of Post-Operative Patients Responding by Treatment Group Modified-Intent-to-Treat population Studies 090 - 091

Study 090	**Aprepitant 40 mg PO (N=248)**		**Ondansetron 4 mg IV (N=246)**		**Aprepitant vs Ondansetron**	
	n/m	**(%)**	**n/m**	**(%)**	**OR**	**95% C.I.**
Complete Response (0-24 hours)[†]	111/248	(44.8)	104/246	(42.3)	1.1	(0.77; 1.57)
No Vomiting (0-24 Hours)	223/248	(89.9)	181/246	(73.6)	3.2	p-val < 0.001
Study 091	**Aprepitant 40 mg PO (N=293)**		**Ondansetron 4 mg IV (N=280)**		**Aprepitant vs Ondansetron**	
	n/m	**(%)**	**n/m**	**(%)**	**OR**	**95% C.I.**
Complete Response (0-24 hours) [†]	187/293	(63.8)	154/280	(55.0)	1.4	(1.02; 2.01)
No Vomiting (0-24 Hours)	246/293	(84.0)	200/280	(71.4)	2.1	p-val < 0.001

[†] Complete Response = No vomiting and no use of rescue.

[‡] Estimated odds ratio for Aprepitant 40 mg versus Ondansetron 4 mg. The lower bound of CI > 0.65 means that Aprepitant 40 mg is non-inferior to Ondansetron 4 mg. A value of >1 means that Aprepitant 40 mg is better than Ondansetron4 mg.

The model included terms for treatment and investigative sites.

n/m= Number of patients with desired response/number of patients included in analysis.

CI = Confidence Interval.

Results presented in the table were obtained by use of a logistics model with terms for treatment and investigative sites. For the No Vomiting endpoint, an additional analysis was performed for time to first event, where patients who received rescue medication were censored at the time of rescue. In study 090, results of this analysis show that the reduction in risk for a vomiting episode over the 0 to 24 hour period with aprepitant 40 mg relative to ondansetron 4 mg was 61.9% (95% C.I.: **32.1%, 78.6%).** In study 091, results of this analysis show that reduction in risk for a vomiting episode over the 0 to 24 hour period with aprepitant 40 mg relative to ondansetron 4 mg was 48.7% (95% C.I.: **23.6%, 65.5%)**.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The mean absolute oral bioavailability of aprepitant (125 or 80 mg capsules) is approximately 60% to 65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}).

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.

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.

Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

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.

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.

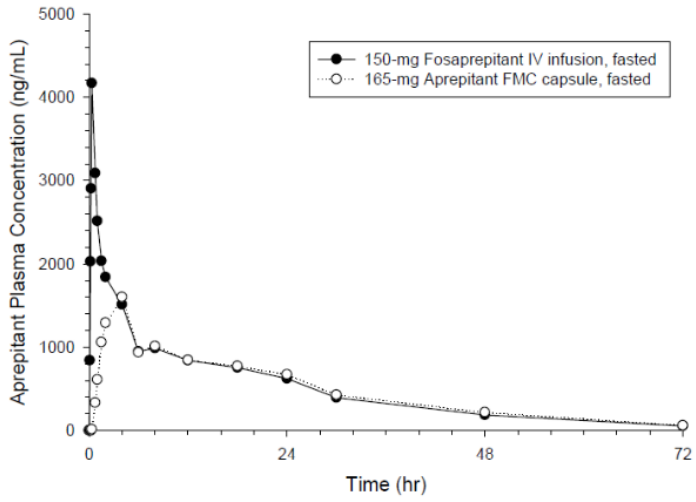
As shown in the table below, following oral administration of a single 165 mg dose of aprepitant, in the fasted state, the $AUC_{0-\infty}$ of aprepitant was 32.5 µg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 1.67 µg/mL, as compared to aprepitant exposures in the fed state when a single 165 mg dose of aprepitant was given with a standard light (low-fat) breakfast, and when given with a standard high-fat breakfast.

Plasma Aprepitant Pharmacokinetic Parameters	Fasted State	Fed State	
		Light (low- fat) Breakfast	High-fat Breakfast
$AUC_{0-\infty}$ (µg•hr/mL)	32.5	35.2	47.8
C_{max} (µg/mL)	1.67	1.73	2.21

Oral administration of the 165 mg dose of aprepitant with a standard light (low-fat) breakfast and a high-fat breakfast resulted in up to an 8% and 47% increase in $AUC_{0-\infty}$ of aprepitant, respectively. It is recommended that aprepitant 165 mg be taken fasted or with a light (low fat) meal to minimise the potential for drug interactions (see section **4.5 Interactions with other medicines and other forms of interactions**).

The geometric mean ratio (GMR) and nominal 95% confidence interval (CI) for aprepitant $AUC_{0-\infty}$ for 165 mg oral aprepitant / 150 mg IV fosaprepitant was 0.93 (0.84, 1.02) which demonstrated that a single 165 mg dose of aprepitant taken in the fasted state was $AUC_{0-\infty}$ -equivalent to a single 150 mg dose (1 mg/mL) of the IV prodrug, fosaprepitant, when infused over 20 minutes. Mean plasma concentrations following single doses are depicted in **Figure 6**.

Figure 6: Mean Plasma Concentration of Aprepitant Following 165 mg Oral Aprepitant and 150 mg IV Fosaprepitant



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 rabbits, 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 Pharmacodynamic properties - Mechanism of action**).

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.

Excretion

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.

Special Populations

Aprepitant 165 mg pharmacokinetics have not been evaluated in special populations. No clinically relevant differences in aprepitant pharmacokinetics are expected.

Gender

Following oral administration of a single 125 mg dose of aprepitant, the C_{max} for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 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 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 is necessary in elderly patients.

Race

Following oral administration of a single 125 mg dose of aprepitant, the $AUC_{0\text{-}24hr}$ is approximately 25% and 29% higher in Hispanics as compared with Caucasians and Blacks, respectively. The C_{max} is 22% and 31% higher in Hispanics as compared with Caucasians and Blacks, respectively. These differences are not considered clinically meaningful. No dosage adjustment for aprepitant is necessary based on race.

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%. However, due to decreases in protein binding of aprepitant in ESRD patients, the AUC of pharmacologically active unbound drug was not significantly affected as 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 is necessary in patients with severe renal insufficiency or in patients with ESRD undergoing haemodialysis, based on the pharmacokinetics of aprepitant in these patients, although no clinical studies have been conducted to determine whether efficacy is affected.

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 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).

Paediatric Patients

The pharmacokinetics of aprepitant have not been evaluated in patients below 18 years of age.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Aprepitant was not genotoxic in the *in vitro* microbial and TK6 human lymphoblastoid cell mutagenesis assays, alkaline elution/rat hepatocyte DNA strand break test and chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus assay.

Carcinogenicity

Carcinogenicity studies of approximately 2 years duration were conducted in mice and rats with oral aprepitant. In mice, aprepitant was not carcinogenic at doses up to 500 mg/kg/day (approximately 2 times the adult human dose based on systemic exposure). Rats developed hepatocellular adenomas at a dose of 25 mg/kg twice daily (females) and 125 mg/kg twice daily (males), thyroid follicular cell adenomas at a dose of 125 mg/kg twice daily (females and males), and thyroid follicular cell carcinomas at a dose of 125 mg/kg twice daily (males). Systemic exposures at these doses in rats were approximately equivalent to or lower than exposures in humans at the recommended dose. Tumours of these types are considered to be a 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. Consideration of the mechanisms involved in the development of these tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of aprepitant.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each capsule of APREPITANT APOTEX contains the following inactive ingredients: sucrose, microcrystalline cellulose, hypromellose and poloxamer.

The hard gelatin capsules contain the following inactive ingredients: gelatin, titanium dioxide and sodium lauryl sulfate.

The 40 mg capsule shell also contains iron oxide yellow, the 125 mg capsule shell also contains iron oxide red and the 165 mg capsule shell also contains indigo carmine aluminium lake. The capsules are printed with OPACODE monogramming ink S-1-17823 BLACK.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

APREPITANT APOTEX capsules should be stored below 25°C in their original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister Pack (PA/Al/PVC/Al).
APREPITANT APOTEX comes in pack sizes containing:
1x 165 mg capsules
1x 125mg + 2x 80 mg capsules
2x 80mg capsule
1x40mg capsule

***** Not all pack size may be marketed.

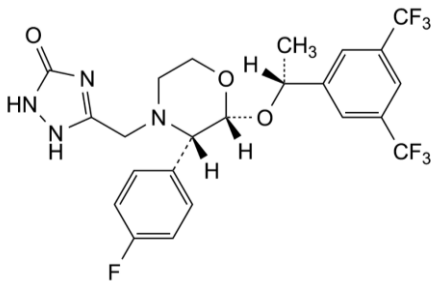
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Aprepitant is 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*-1,2,4-triazol-3-one.



Molecular formula: $C_{23}H_{21}F_7N_4O_3$

Molecular mass: 534.4

CAS number

CAS number: 170729-80-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Apotex Pty Ltd

16 Giffnock Avenue

Macquarie Park NSW 2113

Australia

Tel: +61 2 8877 8333
Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

11 June 2019

10 DATE OF REVISION

n/a

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	New