APREPILOR TRIO

1. NAME OF THE MEDICINAL PRODUCT

APREPILOR TRIO 80 mg + 125 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each capsule contains 125 mg of sucrose (in the 125 mg capsule).
Excipient with known effect
Each capsule contains 80 mg of sucrose (in the 80 mg capsule).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The 125 mg capsule is size 1 capsule and has an opaque pink cap and an opaque white body printed with “125 mg” in black ink.
The 80 mg capsule is size 2 capsule and has an opaque white cap and an opaque white body printed with “80 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12.

APREPILOR TRIO 125 mg/80 mg is given as part of combination therapy (see section 4.2).

4.2 Posology and method of administration

Posology

Adults
APREPILOR TRIO is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose is 125 mg orally once daily one hour before start of chemotherapy on Day 1 and 80 mg orally once daily on Days 2 and 3 in the morning.

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

Highly Emetogenic Chemotherapy Regimen

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

Moderately Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3
aprepitant	125 mg orally	80 mg orally	80 mg orally
Dexamethasone	12 mg orally	none	none
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists. See the product information 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 accounts for

active substance interactions.

Paediatric population
Adolescents (aged 12 through 17 years)
APREPILOR TRIO is given for 3 days as part of a regimen that includes a 5-HT_3 antagonist. The recommended dose of capsules of APREPILOR TRIO is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. APREPILOR TRIO is administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, APREPILOR TRIO should be administered in the morning. See the Summary of Product Characteristics (SmPC) for the selected 5-HT_3 antagonist for appropriate dosing information. If a corticosteroid, such as dexamethasone, is co-administered with APREPILOR TRIO, the dose of the corticosteroid should be administered at 50% of the usual dose (see sections 4.5 and 5.1).

The safety and efficacy of the 80 mg and 125 mg capsules have not been demonstrated in children less than 12 years of age. No data are available.

General
Efficacy data in combination with other corticosteroids and 5-HT_3 antagonists are limited. For additional information on the co-administration with corticosteroids, see section 4.5. Please refer to the SmPC of co-administered 5-HT_3 antagonist medicinal products.

Special populations
Elderly (≥ 65 years)
No dose adjustment is necessary for the elderly (see section 5.2).

Gender
No dose adjustment is necessary based on gender (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment or for patients with end stage renal disease undergoing haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. Aprepitant should be used with caution in these patients (see sections 4.4 and 5.2).

Method of administration
The hard capsule should be swallowed whole.
APREPILOR TRIO may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Co-

administration with pimozide or cisapride (see section 4.5).

4.4 Special warnings and precautions for use

Patients with moderate to severe hepatic impairment
There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. APREPILOR TRIO should be used with caution in these patients (see section 5.2).

CYP3A4 interactions
APREPILOR TRIO should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, ergot alkaloid derivatives, fentanyl, and quinidine (see section 4.5). Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination might result in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)
In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely during treatment with APREPILOR TRIO and for 14 days following each 3-day course of APREPILOR TRIO (see section 4.5).

Co-administration with hormonal contraceptives
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of APREPILOR TRIO. Alternative non-hormonal back-up methods of contraception should be used during treatment with APREPILOR TRIO and for 2 months following the last dose of APREPILOR TRIO (see section 4.5).

Excipients
APREPILOR TRIO capsules contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose- galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Sodium
APREPILOR TRIO contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of aprepitant on the pharmacokinetics of other active substances

CYP3A4 inhibition

As a moderate inhibitor of CYP3A4, aprepitant (125 mg/80 mg) can increase plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of orally administered CYP3A4 substrates may increase up to approximately 3-fold during the 3-day treatment with APREPILOR TRIO; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. APREPILOR TRIO must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride (see section 4.3). Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. Caution is advised during concomitant administration of APREPILOR TRIO and orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see section 4.4).

Corticosteroids

Dexamethasone: The usual oral dexamethasone dose should be reduced by approximately 50% when co-administered with aprepitant 125 mg/80 mg regimen. The dose of dexamethasone in chemotherapy induced nausea and vomiting clinical trials was chosen to account for active substance interactions (see section 4.2). Aprepitant, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and aprepitant when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, 2.2-fold on Days 1 and 5.

Methylprednisolone: The usual intravenously administered methylprednisolone dose should be reduced approximately 25%, and the usual oral methylprednisolone dose should be reduced approximately 50% when co-administered with aprepitant 125 mg/80 mg regimen. aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.3-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was co-administered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

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

Chemotherapeutic medicinal products

In pharmacokinetic studies, aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, did not influence the pharmacokinetics of docetaxel administered intravenously on Day 1 or vinorelbine administered intravenously on Day 1 or Day 8. Because the effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates, an interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g. etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolized primarily or partly by CYP3A4 (see section 4.4). Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration.

Immunosuppressants

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

Midazolam

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

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

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 2 mg midazolam was given intravenously prior to the administration of the 3-day regimen of aprepitant and on Days 4, 8, and 15. Aprepitant increased the AUC of midazolam 25% on Day 4 and decreased the AUC of midazolam 19% on Day 8 and 4% on Day 15. These effects were not considered clinically important.

In a third study with intravenous and oral administration of midazolam, aprepitant was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, together with ondansetron 32 mg Day 1, dexamethasone 12 mg Day 1 and 8 mg Days 2-4. This combination (i.e. aprepitant, ondansetron and dexamethasone) decreased the AUC of oral midazolam 16% on Day 6, 9% on Day 8, 7% on Day 15 and 17% on Day 22. These effects were not considered clinically important.

An additional study was completed with intravenous administration of midazolam and aprepitant. Intravenous 2 mg midazolam 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.

Induction

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

Warfarin
In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with aprepitant and for 2 weeks following each 3-day course of aprepitant for chemotherapy induced nausea and vomiting (see section 4.4). When a single 125 mg dose of aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilised on chronic warfarin therapy, there was no effect of aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3; however, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in INR 5 days after completion of treatment with aprepitant.

Tolbutamide
Aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of aprepitant and on Days 4, 8, and 15.

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

In a clinical study, single doses of an oral contraceptive containing ethinyl estradiol and norethindrone were administered on Days 1 through 21 with aprepitant, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg intravenously on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. During days 9 through 21 in this study, there was as much as a 64% decrease in ethinyl estradiol trough concentrations and as much as a 60% decrease in norethindrone trough concentrations.

5-HT_3 antagonists
In clinical interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of other medicinal products on the pharmacokinetics of aprepitant
Concomitant administration of aprepitant with active substances that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, and protease inhibitors) should be approached cautiously, as the combination is expected to result several-fold in increased plasma concentrations of aprepitant (see section 4.4).

Concomitant administration of aprepitant with active substances that strongly induce CYP3A4 activity (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant. Concomitant administration of aprepitant with herbal preparations containing St. John's Wort (*Hypericum perforatum)* is not recommended.

Ketoconazole
When a single 125 mg dose of aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold.

Rifampicin
When a single 375 mg dose of aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampicin, a strong CYP3A4 inducer, the AUC of aprepitant decreased 91% and the mean terminal half-life decreased 68%.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of aprepitant. Alternative non-hormonal back-up methods of contraception should be used during treatment with aprepitant and for 2 months following the last dose of aprepitant (see sections 4.4 and 4.5).

Pregnancy
For aprepitant no clinical data on exposed pregnancies are available. The potential for reproductive toxicity of aprepitant has not been fully characterised, since exposure levels above the therapeutic exposure in humans at the 125 mg/80 mg dose could not be attained in animal studies. These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential effects on reproduction of alterations in neurokinin regulation are unknown. Aprepitant should not be used during pregnancy unless clearly necessary.

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

Fertility
The potential for effects of aprepitant on fertility has not been fully characterised because exposure levels above the therapeutic exposure in humans could not be attained in animal studies. These fertility studies did not indicate direct or indirect harmful effects with respect to mating performance, fertility, embryonic/foetal development, or sperm count and motility (see section 5.3).

4.7 Effects on ability to drive and use machines

APREPILOR TRIO may have minor influence on the ability to drive, cycle and use machines. Dizziness and fatigue may occur following administration of APREPILOR TRIO (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The safety profile of aprepitant was evaluated in approximately 6,500 adults in more than 50 studies and 184 children and adolescents in 2 pivotal paediatric clinical trials.

The most common adverse reactions reported at a greater incidence in adults treated with the aprepitant regimen than with standard therapy in patients receiving Highly Emetogenic Chemotherapy (HEC) were: hiccups (4.6% versus 2.9%), alanine aminotransferase (ALT) increased (2.8% versus 1.1%), dyspepsia (2.6% versus 2.0%), constipation (2.4% versus 2.0%), headache (2.0% versus 1.8%), and decreased appetite (2.0% versus 0.5%). The most common adverse reaction reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy in patients receiving Moderately Emetogenic Chemotherapy (MEC) was fatigue (1.4% versus 0.9%).

The most common adverse reactions reported at a greater incidence in paediatric patients treated with the aprepitant regimen than with the control regimen while receiving emetogenic cancer chemotherapy were hiccups (3.3% versus 0.0%) and flushing (1.1% versus 0.0%).

Tabulated list of adverse reactions
The following adverse reactions were observed in a pooled analysis of the HEC and MEC studies at a greater incidence with aprepitant than with standard therapy in adults or paediatric patients or in post-marketing use. The frequency categories given in the table are based on the studies in adults; the observed frequencies in the paediatric studies were similar or lower, unless shown in the table. Some less common ADRs in the adult population were not observed in the paediatric studies.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

*Nausea and vomiting were efficacy parameters in the first 5 days of post-chemotherapy treatment and were reported as adverse reactions only thereafter.

Description of selected adverse reactions

The adverse reactions profiles in adults in the Multiple-Cycle extension of HEC and MEC studies for up to 6 additional cycles of chemotherapy were generally similar to those observed in Cycle 1.

In an additional active-controlled clinical study in 1,169 adult patients receiving aprepitant and HEC, the adverse reactions profile was generally similar to that seen in the other HEC studies with aprepitant.

Additional adverse reactions were observed in adult patients treated with aprepitant for postoperative nausea and vomiting (PONV) and a greater incidence than with ondansetron: abdominal pain upper, bowel sounds abnormal, constipation*, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, sub-ileus*, visual acuity reduced, wheezing.
*Reported in patients taking a higher dose of aprepitant.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Health Product Pharmacovigilance Center at: http://thaihpvc.fda.moph.go.th.

4.9 Overdose

In the event of overdose, APREPILOR TRIO should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, emesis induced by a medicinal product may not be effective.

Aprepitant cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, ATC code: A04AD12

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK_1) receptors. 3-

day regimen of aprepitant in adults
In 2 randomised, double-blind studies encompassing a total of 1,094 adult patients receiving chemotherapy that included cisplatin ≥ 70 mg/m^2, aprepitant in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with a standard regimen (placebo plus ondansetron 32 mg intravenously administered on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4). Although a 32 mg intravenous dose of ondansetron was used in clinical trials, this is no longer the recommended dose. See the product information for the selected 5-HT_3 antagonist for appropriate dosing information.

Efficacy was based on evaluation of the following composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) primarily during Cycle 1. The results were evaluated for each individual study and for the 2 studies combined.
A summary of the key study results from the combined analysis is shown in Table 1.

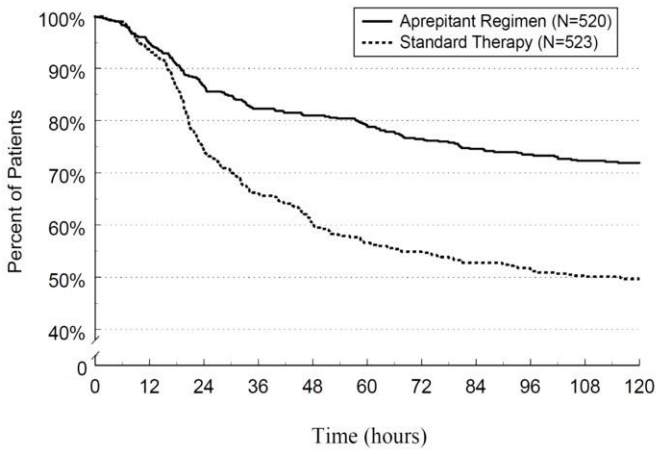
Table 1
Percent of adult patients receiving Highly Emetogenic Chemotherapy responding by treatment group and phase – Cycle 1

COMPOSITE MEASURES	Aprepitant regimen (N=521) † %	Standard therapy (N=524) † %	Differences* %	(95% CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	67.7	47.8	19.9	(14.0, 25.8)
0-24 hours	86.0	73.2	12.7	(7.9, 17.6)
25-120 hours	71.5	51.2	20.3	(14.5, 26.1)
INDIVIDUAL MEASURES				
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	71.9	49.7	22.2	(16.4, 28.0)
0-24 hours	86.8	74.0	12.7	(8.0, 17.5)
25-120 hours	76.2	53.5	22.6	(17.0, 28.2)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	72.1	64.9	7.2	(1.6, 12.8)
25-120 hours	74.0	66.9	7.1	(1.5, 12.6)

* The confidence intervals were calculated with no adjustment for gender and concomitant chemotherapy, which were included in the primary analysis of odds ratios and logistic models.
† One patient in the Aprepitant regimen only had data in the acute phase and was excluded from the overall and delayed phase analyses; one patient in the Standard regimen only had data in the delayed phase and was excluded from the overall and acute phase analyses.

The estimated time to first emesis in the combined analysis is depicted by the Kaplan-Meier plot in Figure 1.

Figure 1
Percent of adult patients receiving Highly Emetogenic Chemotherapy who remain emesis free over time – Cycle 1



Statistically significant differences in efficacy were also observed in each of the 2 individual studies.

In the same 2 clinical studies, 851 adult patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was apparently maintained during all cycles.

In a randomised, double-blind study in a total of 866 adult patients (864 females, 2 males) receiving chemotherapy that included cyclophosphamide 750-1,500 mg/m^2; or cyclophosphamide 500-1,500 mg/m^2 and doxorubicin ($\leq$ 60 mg/m^2) or epirubicin ($\leq$ 100 mg/m^2), aprepitant in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with 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).

Efficacy was based on evaluation of the composite measure: complete response (defined as no emetic episodes and no use of rescue therapy) primarily during Cycle 1.

A summary of the key study results is shown in Table 2.

Table 2
Percent of adult patients responding by treatment group and phase - Cycle 1
Moderately Emetogenic Chemotherapy

COMPOSITE MEASURES	Aprepitant regimen (N=433) † %	Standard therapy (N=424) † %	Differences* %	(95% CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	50.8	42.5	8.3	(1.6, 15.0)
0-24 hours	75.7	69.0	6.7	(0.7, 12.7)
25-120 hours	55.4	49.1	6.3	(-0.4, 13.0)
INDIVIDUAL MEASURES				
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	75.7	58.7	17.0	(10.8, 23.2)
0-24 hours	87.5	77.3	10.2	(5.1, 15.3)
25-120 hours	80.8	69.1	11.7	(5.9, 17.5)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	60.9	55.7	5.3	(-1.3, 11.9)
0-24 hours	79.5	78.3	1.3	(-4.2, 6.8)
25-120 hours	65.3	61.5	3.9	(-2.6, 10.3)

* The confidence intervals were calculated with no adjustment for age category (< 55 years, ≥ 55 years) and investigator group, which were included in the primary analysis of odds ratios and logistic models.
† One patient in the Aprepitant regimen only had data in the acute phase and was excluded from the overall and delayed phase analyses.

In the same clinical study, 744 adult patients continued into the Multiple-Cycle extension for up to 3 additional cycles of chemotherapy. The efficacy of the aprepitant regimen was apparently maintained during all cycles.

In a second multicentre, randomised, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 adult patients (652 females, 196 males) receiving a chemotherapy regimen that included any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide intravenously (< 1,500 mg/m^2); or cytarabine intravenously (> 1 g/m^2). 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 in combination with an ondansetron/dexamethasone regimen (see section 4.2) was compared with standard therapy (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).

Efficacy was based on the evaluation of the following primary and key secondary endpoints: No vomiting in the overall period (0 to 120 hours post-chemotherapy), evaluation of safety and tolerability of the aprepitant regimen for chemotherapy induced nausea and vomiting (CINV), and complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy). Additionally, no significant nausea in the overall period (0 to 120 hours post-chemotherapy) was evaluated as an exploratory endpoint, and in the acute and delayed phases as a post-hoc analysis.

A summary of the key study results is shown in Table 3.

Table 3
Percent of adult patients responding by treatment group and phase for Study 2 – Cycle 1
Moderately Emetogenic Chemotherapy

COMPOSITE MEASURES	Aprepitant regimen (N=425) %	Standard therapy (N=406) %	Differences* %	(95% CI)
Complete response (no emesis and no rescue therapy)				
Overall (0-120 hours)	68.7	56.3	12.4	(5.9, 18.9)
0-24 hours	89.2	80.3	8.9	(4.0, 13.8)
25-120 hours	70.8	60.9	9.9	(3.5, 16.3)
No emesis (no emetic episodes regardless of use of rescue therapy)				
Overall (0-120 hours)	76.2	62.1	14.1	(7.9, 20.3)
0-24 hours	92.0	83.7	8.3	(3.9, 12.7)
25-120 hours	77.9	66.8	11.1	(5.1, 17.1)
No significant nausea (maximum VAS < 25 mm on a scale of 0-100 mm)				
Overall (0-120 hours)	73.6	66.4	7.2	(1.0, 13.4)
0-24 hours	90.9	86.3	4.6	(0.2, 9.0)
25-120 hours	74.9	69.5	5.4	(-0.7, 11.5)

*The confidence intervals were calculated with no adjustment for gender and region, which were included in the primary analysis using logistic models.

The benefit of aprepitant combination therapy in the full study population was mainly driven by the results observed in patients with poor control with the standard regimen such as in women, even though the results were numerically better regardless of age, tumour type or gender. Complete response to the aprepitant regimen and standard therapy, respectively, was reached in 209/324 (65%) and 161/320 (50%) in women and 83/101 (82%) and 68/87 (78%) of men.

Paediatric population

In a randomised, double-blind, active comparator-controlled clinical study that included 302 children and adolescents (aged 6 months to 17 years) receiving moderately or highly emetogenic chemotherapy, the aprepitant regimen was compared to a control regimen for the prevention of CINV.

The efficacy of the aprepitant regimen was evaluated in a single cycle (Cycle 1). Patients had the opportunity to receive open-label aprepitant in subsequent cycles (Optional Cycles 2-6); however efficacy was not assessed in these optional cycles. The aprepitant regimen for adolescents aged 12 through 17 years (n=47) consisted of aprepitant capsules 125 mg orally on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron on Day 1. The aprepitant regimen for children aged 6 months to less than 12 years (n=105) consisted of aprepitant powder for oral suspension 3.0 mg/kg (up to 125 mg) orally on Day 1 and 2.0 mg/kg (up to 80 mg) orally on Days 2 and 3 in combination with ondansetron on Day 1. The control regimen in adolescents aged 12 through 17 years (n=48) and children aged 6 months to less than 12 years (n=102) consisted of placebo for aprepitant on Days 1, 2 and 3 in combination with ondansetron on Day 1. Aprepitant or placebo and ondansetron were administered 1 hour and 30 minutes prior to initiation of chemotherapy, respectively. Intravenous dexamethasone was permitted as part of the antiemetic regimen for paediatric patients in both age groups, at the discretion of the physician. A dose reduction (50%) of dexamethasone was required for paediatric patients receiving aprepitant. No dose reduction was required for paediatric patients receiving the control regimen. Of the paediatric patients, 29% in the aprepitant regimen and 28% in the control regimen used dexamethasone as part of the regimen in Cycle 1.

The antiemetic activity of aprepitant was evaluated over a 5-day (120 hour) period following the initiation of chemotherapy on Day 1. The primary endpoint was complete response in the delayed phase (25 to 120 hours following initiation of chemotherapy) in Cycle 1. A summary of the key study results are shown in Table 4.

Table 4

Number (%) of paediatric patients with complete response and no vomiting by treatment group and phase – Cycle 1 (Intent to treat population)

	Aprepitant regimen n/m (%)	Control regimen n/m (%)
PRIMARY ENDPOINT		
Complete response* – Delayed phase	77/152 (50.7)†	39/150 (26.0)
OTHER PRESPECIFIED ENDPOINTS		
Complete response* – Acute phase	101/152 (66.4)‡	78/150 (52.0)
Complete response* – Overall phase	61/152 (40.1)†	30/150 (20.0)
No vomiting§ – Overall phase	71/152 (46.7)†	32/150 (21.3)

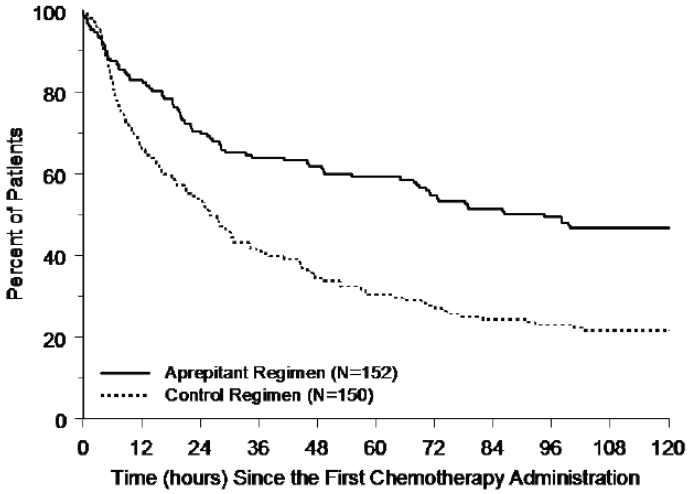
*Complete response = No vomiting or retching or dry heaves and no use of rescue medication.
†p< 0.01 when compared to control regimen
‡p< 0.05 when compared to control regimen
§No vomiting = No vomiting or retching or dry heaves
n/m = Number of patients with desired response/number of patients included in time point.
Acute phase: 0 to 24 hours following initiation of chemotherapy.
Delayed phase: 25 to 120 hours following initiation of chemotherapy.
Overall phase: 0 to 120 hours following initiation of chemotherapy.

The estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen (estimated median time to first vomiting was 94.5 hours) compared with the control regimen group (estimated median time to first vomiting was 26.0 hours) as depicted in the Kaplan-Meier curves in Figure 2.

Figure 2

Time to first vomiting episode from start of chemotherapy administration - paediatric patients in the overall phase-Cycle 1 (Intent to treat

population)



An analysis of efficacy in subpopulations in Cycle 1 demonstrated that, regardless of age category, gender, use of dexamethasone for antiemetic prophylaxis, and emetogenicity of chemotherapy, the aprepitant regimen provided better control than the control regimen with respect to the complete response endpoints.

5.2 Pharmacokinetic properties

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

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

The pharmacokinetics of aprepitant is non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26% greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state.

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} (mean ± SD) was 19.6 ± 2.5 µg·h/mL and 21.2 ± 6.3 µg·h/mL on Days 1 and 3, respectively. C_{max} was 1.6 ± 0.36 µg/mL and 1.4 ± 0.22 µg/mL on Days 1 and 3, respectively.

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

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

Elimination
Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. Following a single intravenously administered 100 mg dose of [^{14}C]-fosaprepitant, a prodrug for aprepitant, to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in faeces.

The plasma clearance of aprepitant is dose-dependent, decreasing with increased dose and ranged from approximately 60 to 72 mL/min in the therapeutic dose range. The terminal half-life ranged from approximately 9 to 13 hours.

Pharmacokinetics in special population
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_{0-24hr} 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 dose adjustment for aprepitant is necessary in elderly patients.

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 dose adjustment for aprepitant is necessary based on gender.

Hepatic impairment: Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a clinically relevant extent. No dose adjustment is necessary for patients with mild hepatic impairment. Conclusions regarding the influence of moderate hepatic impairment (Child-Pugh class B) on aprepitant pharmacokinetics cannot be drawn from available data. There are no clinical or

pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment: A single 240 mg dose of aprepitant was administered to patients with severe renal impairment (CrCl<30 mL/min) and to patients with end stage renal disease (ESRD) requiring haemodialysis.

In patients with severe renal impairment, the $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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 aprepitant was not significantly affected in patients with renal impairment 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 dose adjustment for aprepitant is necessary for patients with renal impairment or for patients with ESRD undergoing haemodialysis.

Paediatric population: As part of a 3-day regimen, dosing of aprepitant capsules (125/80/80-mg) in adolescent patients (aged 12 through 17 years) achieved an AUC_{0-24hr} above 17 μg•hr/mL on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.4 μg/mL in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.3 μg/mL on Day 1, occurring at approximately 4 hours. As part of a 3-day regimen, dosing of aprepitant powder for oral suspension (3/2/2-mg/kg) in patients aged 6 months to less than12 years achieved an AUC_{0-24hr} above 17 μg•hr/mL on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.1 μg/mL in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.2 μg/mL on Day 1, occurring between 5 and 7 hours.

A population pharmacokinetic analysis of aprepitant in paediatric patients (aged 6 months through 17 years) suggests that gender and race have no clinically meaningful effect on the pharmacokinetics of aprepitant.

Relationship between concentration and effect
Using a highly specific NK_1-receptor tracer, positron emission tomography (PET) studies in healthy young men have shown that aprepitant penetrates into the brain and occupies NK_1 receptors in a dose- and plasma-concentration-dependent manner. Aprepitant plasma concentrations achieved with the 3-day regimen of aprepitant in adults are predicted to provide greater than 95% occupancy of brain NK_1 receptors.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. However, it should be noted that systemic exposure in rodents was similar or even lower than therapeutic exposure in humans at the 125 mg/80 mg dose. In particular, although no adverse effects were noted in reproduction studies at human exposure levels, the animal exposures are not sufficient to make an adequate risk assessment in man.

In a juvenile toxicity study in rats treated from post natal day 10 to day 63 aprepitant led to an earlier vaginal opening in females from 250 mg/kg b.i.d. and to a delayed preputial separation in males, from 10 mg/kg b.i.d. There were no margins to clinically relevant exposure. There were no treatment-related effects on mating, fertility or embryonic/foetal survival, and no pathological changes in the reproductive organs. In a juvenile toxicity study in dogs treated from post natal day 14 to day 42, a decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and oedema of vaginal tissues were seen in females from 4 mg/kg/day. There were no margins to clinically relevant exposure of aprepitant. For short term treatment according to recommended dose regimen these findings are considered unlikely to be clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
hydroxypropylcellulose
sodium laurilsulfate
sucrose
cellulose, microcrystalline.

Capsule shell (125 mg)
Titanium dioxide (E 171)
Red iron oxide (E 172)
Gelatin

Capsule shell (80 mg)
Titanium dioxide (E 171)
Gelatin

Printink ink:
Shellac
Ammonia solution, concentrated
Propylene glycol
Potassium hydroxide
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PA/Aluminium/PVC/Aluminium blister containing one 125 mg capsule and two 80 mg capsules.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

American Taiwan Biopharm Co., Ltd.
No. 1, Eastwater Bldg., 16th Floor,
Soi Vibhavadi-Rangsit 5, Vibhavadi-Rangsit Rd.,
Chomphon, Chatuchak, Bangkok, Thailand. 10900

8. MARKETING AUTHORISATION NUMBER

1C 15xxx/65 (NG)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

DD/MM/2022

10. DATE OF REVISION OF THE TEXT

12/2023