

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

EMVOID

1. Generic Name

Combipack of Aprepitant Capsules I.P. 125 mg & 80 mg

2. Qualitative and quantitative composition

Each combipack contains:

(A) Aprepitant Capsules I.P. 125 mg

1 Capsule

Each hard gelatin capsule contains:

Aprepitant.....125 mg

Approved colours used in capsule shell.

(B) Aprepitant Capsules I.P. 80 mg

2 Capsules

Each hard gelatin capsule contains:

Aprepitant.....80 mg

Approved colours used in capsule shell.

The excipients used are Mannitol, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Hydroxy propyl cellulose, Purified Water.

3. Dosage form and strength

Dosage form: Capsules

Strength: 125mg/80mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for chemotherapy induced nausea & vomiting.

4.2 Posology and method of administration

Posology

Adults

Emvoid capsules are given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT₃ 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
Emvoid	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
Emvoid	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)

EMVOID is given for 3 days as part of a regimen that includes a 5-HT₃ antagonist. The recommended dose of capsules of EMVOID is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. EMVOID administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMVOID should be administered in the morning. See the Summary of Product Characteristics (SmPC) for the selected 5-HT₃ antagonist for appropriate dosing information. If a corticosteroid, such a dexamethasone, is co-administered with EMVOID, 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. Refer to the powder for oral suspension SmPC for appropriate dosing in infants, toddlers and children aged 6 months to less than 12 years.

General

Efficacy data in combination with other corticosteroids and 5-HT₃ 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-HT₃ antagonist medicinal products.

Special populations

Elderly (≥ 65 years)

No dose adjustment is necessary for the elderly.

Gender

No dose adjustment is necessary based on gender.

Renal impairment

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

Hepatic impairment

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

Method of administration

The hard capsule should be swallowed whole.

EMVOID may be taken with or without food.

4.3 Contraindications

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

Co-administration with pimozone, terfenadine, astemizole 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. EMVOID should be used with caution in these patients.

CYP3A4 interactions

EMVOID 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 EMVOID and for 14 days following each 3-day course of EMVOID (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 EMVOID. Alternative non-hormonal back-up methods of contraception should be used during treatment with EMVOID and for 2 months following the last dose of EMVOID (see section 4.5).

Excipients

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

4.5 Drugs interactions

Aprepitant (125 mg/80 mg) is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with EMVOID, CYP3A4 is inhibited. After the end of treatment, EMVOID 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 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 EMVOID; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. EMVOID must not be used concurrently with pimozone, 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 EMVOID 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 EMVOID 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). EMVOID, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and EMVOID 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 EMVOID 125 mg/80 mg regimen. EMVOID, 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 EMVOID 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, EMVOID 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 EMVOID on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMVOID on the pharmacokinetics of intravenously administered CYP3A4 substrates, an interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g., etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolised primarily or partly by CYP3A4 (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 EMVOID.

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 EMVOID (125 mg/80 mg).

EMVOID 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 EMVOID 125 mg on Day 1 and 80 mg/day on Days 2 to 5.

In another reported study with intravenous administration of midazolam, EMVOID 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 EMVOID and on Days 4, 8, and 15. EMVOID 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 reported study with intravenous and oral administration of midazolam, EMVOID 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. EMVOID, 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 EMVOID. Intravenous 2 mg midazolam was given 1 hour after oral administration of a single dose of EMVOID 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 EMVOID. For CYP2C9 and CYP3A4 substrates, the induction is transient with a maximum effect reached 3-5 days after end of the EMVOID 3-day treatment. The effect is maintained for a few days, thereafter slowly declines and is clinically insignificant by two weeks after end of EMVOID 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 EMVOID and for 2 weeks following each 3-day course of EMVOID for chemotherapy induced nausea and vomiting (see section 4.4). When a single 125 mg dose of EMVOID 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 EMVOID 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 EMVOID

Tolbutamide

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

In a clinical study, single doses of an oral contraceptive containing ethinyl estradiol and norethindrone were administered on Days 1 through 21 with EMVOID, 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-HT₃ 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 EMVOID 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 EMVOID with active substances that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, and phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy of EMVOID. Concomitant administration of EMVOID 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 Use in special populations

Contraception in males and females

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

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.

4.7 Effects on ability to drive and use machines

EMVOID may have minor influence on the ability to drive, cycle and use machines. Dizziness and fatigue may occur following administration of EMVOID.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

System organ class	Adverse reaction	Frequency
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product 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 any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

In the event of overdose, EMVOID 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 Mechanism of Action

Aprepitant is classified as an NK1 antagonist because it blocks signals given off by NK1 receptors. This, therefore, decreases the likelihood of vomiting in patients. NK1 is a G protein-coupled receptor located in the central and peripheral nervous system. This receptor has a dominant ligand known as Substance P (SP). SP is a neuropeptide, composed of 11 amino acids, which sends impulses and messages from the brain. It is found in high concentrations in the vomiting centre of the brain, and, when activated, it results in a vomiting reflex. In addition to this it also plays a key part in the transmission of pain impulses from the peripheral receptors to the central nervous system.

5.2 Pharmacodynamics properties

Pharmacotherapeutic group: Antiemetics and antinauseants, ATC code: A04AD12

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK1) receptors.

3-day regimen of aprepitant in adults

In reported 2 randomised, double-blind studies encompassing a total of 1,094 adult patients receiving chemotherapy that included cisplatin ≥ 70 mg/m², 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-HT₃ 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)

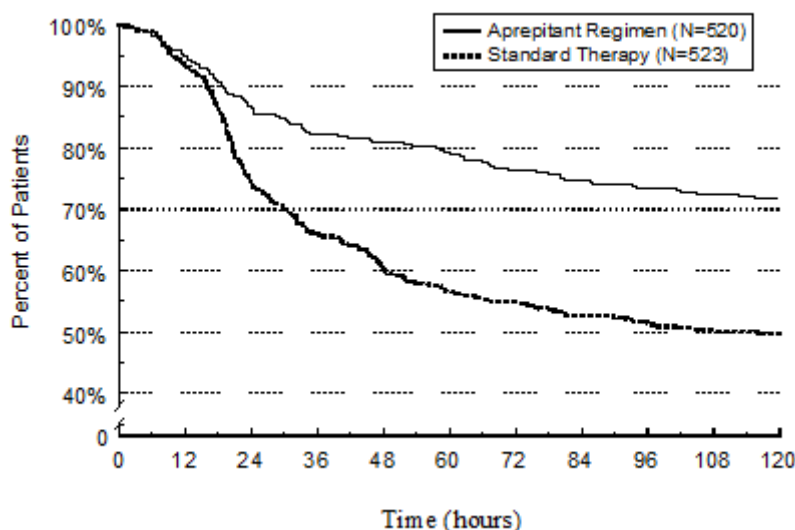
* The confidence intervals were calculated with no adjustment for gender and concomitant chemotherapy, which were included in the primary analysis of odds ratios and logistic models.

† 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 reported 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 reported randomised, double-blind study in a total of 866 adult patients (864 females, 2 males) receiving chemotherapy that included cyclophosphamide 750-1,500 mg/m²; or cyclophosphamide 500-1,500 mg/m² and doxorubicin (≤ 60 mg/m²) or epirubicin (≤ 100 mg/m²), 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/m²); or cytarabine intravenously (> 1 g/m²). 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

	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 EMVOID 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 EMVOID 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. EMVOID 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 EMVOID 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

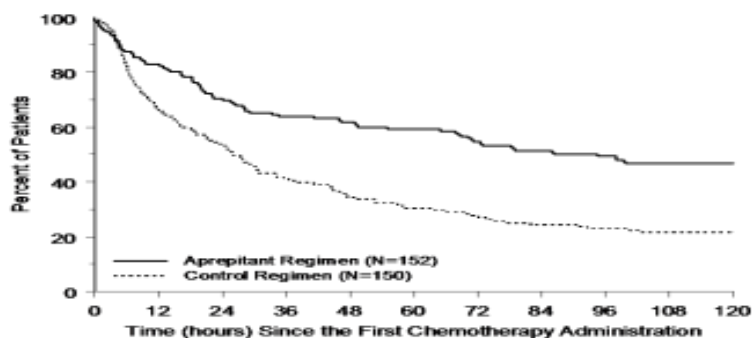
Number (%) of paediatric patients with complete response and no vomiting by treatment group and phase – Cycle 1 (Intent to treat population)

	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.

5.3 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 EMVOID on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} (mean \pm SD) was $19.6 \pm 2.5 \mu\text{g}\cdot\text{h/mL}$ and $21.2 \pm 6.3 \mu\text{g}\cdot\text{h/mL}$ on Days 1 and 3, respectively. C_{max} was $1.6 \pm 0.36 \mu\text{g/mL}$ and $1.4 \pm 0.22 \mu\text{g/mL}$ 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 ($V_{d_{ss}}$) 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 populations

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 EMVOID 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 EMVOID 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 EMVOID 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 $\mu g \cdot hr/mL$ on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.4 $\mu g/mL$ in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.3 $\mu g/mL$ 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 than 12 years achieved an AUC_{0-24hr} above 17 $\mu g \cdot hr/mL$ on Day 1 with concentrations (C_{min}) at the end of Days 2 and 3 above 0.1 $\mu g/mL$ in a majority of patients. The median peak plasma concentration (C_{max}) was approximately 1.2 $\mu g/mL$ 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 NK₁-receptor tracer, positron emission tomography (PET) studies in healthy young men have shown that aprepitant penetrates into the brain and occupies NK₁ receptors in a dose- and plasma-concentration-dependent manner. Aprepitant plasma concentrations achieved with the 3-day regimen of EMVOID in adults are predicted to provide greater than 95 % occupancy of brain NK₁ receptors.

6 Nonclinical properties

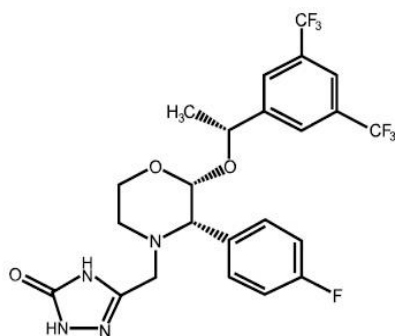
6.1 Animal Toxicology or Pharmacology

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.

7 Description

Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist, an antiemetic agent, chemically described as 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one. Its empirical formula is C₂₃H₂₁F₇N₄O₃, having molecular weight of 534.4 and its structural formula is:



Aprepitant is a white to off-white powder which is sparingly soluble in ethanol (95%); slightly soluble in acetonitrile; practically insoluble in water.

Aprepitant Capsules 80 mg are Size "2" hard gelatin capsules having light pink color body and maroon color cap filled with white to off white color granular powder.

Aprepitant Capsules 125 mg are Size "0" hard gelatin capsules having yellow color body and maroon color cap filled with white to off white color granular powder.

The excipients used are Mannitol, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Hydroxy propyl cellulose, Purified Water.

8 Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Combipack contains 1 capsule of 125 mg and 2 capsules of 80 mg.

8.4 Storage and handing instructions

Store below 30°C, Protect from light and moisture.

Keep out of reach of children.

9 Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What **Emvoid** are and what they are used for

9.2 What you need to know before you use **Emvoid**

9.3 How to use **Emvoid**

9.4 Possible side effects

9.5 How to store **Emvoid**

9.6 Contents of the pack and other information

9.1. What Emvoid are and what they are used for.

EMVOID contains the active substance aprepitant and belongs to a group of medicines called “neurokinin 1 (NK1) receptor antagonists”. The brain has a specific area that controls nausea and vomiting. EMVOID works by blocking signals to that area, thereby reducing nausea and vomiting. EMVOID capsules are used in adults and adolescents from the age of 12 years in combination with other medicines to prevent nausea and vomiting caused by chemotherapy (cancer treatment) that are strong and moderate triggers of nausea and vomiting (such as cisplatin, cyclophosphamide, doxorubicin or epirubicin).

9.2 What you need to know before you use Emvoid

Do not take EMVOID:

- If you or the child is allergic to aprepitant or any of the other ingredients of this medicine.
- With medicines containing pimoziide (used to treat psychiatric illnesses), terfenadine and astemizole (used for hay fever and other allergic conditions), cisapride (used for treating digestive problems). Tell the doctor if you or the child is taking these medicines since the treatment must be modified before you or the child start taking EMVOID.

Warnings and precautions

Talk to the doctor, pharmacist, or nurse before you take EMVOID or give this medicine to the child. Before treatment with EMVOID, tell the doctor if you or the child have liver disease because the liver is important in breaking down the medicine in the body. The doctor may therefore have to monitor the condition of your or the child's liver.

Children and adolescents

Do not give EMVOID 80 mg and 125 mg capsules to children under 12 years of age, because the 80 mg and 125 mg capsules have not been studied in this population.

Other medicines and EMVOID

EMVOID can affect other medicines both during and after treatment with EMVOID. There are some medicines that should not be taken with EMVOID (such as pimoziide, terfenadine, astemizole, and cisapride) or that require a dose adjustment (see also 'Do not take EMVOID').

The effects of EMVOID or other medicines might be influenced if you or the child take EMVOID together with other medicines including those listed below. Please talk to the doctor or pharmacist if you or the child is taking any of the following medicines:

- birth control medicines which can include birth control pills, skin patches, implants, and certain Intrauterine devices (IUDs) that release hormones may not work adequately when taken together with EMVOID. Another or additional non-hormonal form of birth control should be used during treatment with EMVOID and for up to 2 months after using EMVOID,
- Cyclosporine, tacrolimus, sirolimus, everolimus (immunosuppressants),
- Alfentanil, fentanyl (used to treat pain),
- Quinidine (used to treat an irregular heart beat),
- Irinotecan, etoposide, vinorelbine, ifosfamide (medicines used to treat cancer),
- Medicines containing ergot alkaloid derivatives such as ergotamine and diergotamine (used for treating migraines),
- Warfarin, acenocoumarol (blood thinners; blood tests may be required),
- Rifampicin, clarithromycin, telithromycin (antibiotics used to treat infections),
- Phenytoin (a medicine used to treat seizures),
- Carbamazepine (used to treat depression and epilepsy),
- Midazolam, triazolam, phenobarbital (medicines used to produce calmness or help you sleep),
- St. John's Wort (an herbal preparation used to treat depression),
- Protease inhibitors (used to treat HIV infections)

- Ketoconazole except shampoo (used to treat Cushing's syndrome - when the body produces an excess of cortisol),
- Itraconazole, voriconazole, posaconazole (antifungals),
- Nefazodone (used to treat depression),
- Corticosteroids (such as dexamethasone and methylprednisolone),
- Anti-anxiety medicines (such as alprazolam),
- Tolbutamide (a medicine used to treat diabetes).

Tell the doctor or pharmacist if you or the child are taking, have recently taken, or might take any other medicines.

Pregnancy and breast-feeding

This medicine should not be used during pregnancy unless clearly necessary. If you or the child are pregnant or breast-feeding, may be pregnant or are planning to have a baby, ask the doctor for advice before taking this medicine.

For information regarding birth control, see ‘

Other medicines and EMVOID ’.

It is not known whether EMVOID is excreted in human milk; therefore, breast-feeding is not recommended during treatment with this medicine. It is important to tell the doctor if you or the child are breast-feeding or are planning to breast-feed before taking this medicine.

Driving and using machines

It should be taken into account that some people feel dizzy and sleepy after taking EMVOID. If you or the child feels dizzy or sleepy, avoid driving, riding a bicycle or using machines or tools after taking this medicine (see ‘Possible side effects’).

EMVOID contains sucrose

EMVOID capsules contain sucrose. If you or the child have been told by your doctor that you or the child have an intolerance to some sugars, contact the doctor before taking this medicine.

9.3 How to use Emvoid

Always take this medicine or give this medicine to the child exactly as the doctor, pharmacist or nurse has told you. You should check with the doctor, pharmacist or nurse if you are not sure. Always take EMVOID together with other medicines, to prevent nausea and vomiting. After treatment with EMVOID, the doctor may ask you or the child to continue taking other medicines including a corticosteroid (such as dexamethasone) and a ‘5HT3 antagonist’ (such as ondansetron) for preventing nausea and vomiting. Check with the doctor, pharmacist or nurse if you are not sure. The recommended oral dose of EMVOID is Day 1:

- One 125 mg capsule 1 hour before you start your chemotherapy session and Days 2 and 3:
- One 80 mg capsule each day
- If no chemotherapy is given, take EMVOID in the morning.
- If chemotherapy is given, take EMVOID 1 hour before you start your chemotherapy session. EMVOID can be taken with or without food. Swallow the capsule whole with some liquid.

If you take more EMVOID than you should

Do not take more capsules than the doctor recommends. If you or the child has taken too many capsules, contact your doctor immediately.

If you forget to take EMVOID

If you or the child has missed a dose, contact your doctor for advice.

If you have any further questions on the use of this medicine, ask the doctor or pharmacist

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Stop taking EMVOID and see a doctor immediately if you or the child notice any of the following side effects, which may be serious, and for which you or the child may need urgent medical treatment:

- Hives, rash, itching, difficulty breathing or swallowing (frequency not known, cannot be estimated from the available data); these are signs of an allergic reaction.

Other side effects that have been reported are listed below.

Common side effects (may affect up to 1 in 10 people) are:

- constipation, indigestion,
- headache,
- tiredness,
- loss of appetite,
- hiccups,
- Increased amount of liver enzymes in your blood.

Uncommon side effects (may affect up to 1 in 100 people) are:

- dizziness, sleepiness,
- acne, rash,
- anxiousness,
- burping, nausea, vomiting, heartburn, stomach pain, dry mouth, passing wind,
- increased painful or burning urination,
- weakness, generally feeling unwell,
- hot flush/reddening of the face or skin,
- fast or irregular heartbeats,
- Fever with increased risk of infection, lowering of red blood cells.

Rare side effects (may affect up to 1 in 1,000 people) are:

- difficulty thinking, lack of energy, taste disturbance,
- sensitivity of the skin to sun, excessive sweating, oily skin, sores on skin, itching rash, Stevens Johnson syndrome/toxic epidermal necrolysis (rare severe skin reaction),
- euphoria (feeling of extreme happiness), disorientation,
- bacterial infection, fungal infection,
- severe constipation, stomach ulcer, inflammation of the small intestine and colon, sores in mouth, bloating,
- frequent urination, passing more urine than normal, presence of sugar or blood in urine,
- chest discomfort, swelling, change in the manner of walking,
- cough, mucus in back of throat, throat irritation, sneezing, sore throat,

- eye discharge and itching,
- ringing in the ear,
- muscle spasms, muscle weakness,
- excessive thirst,
- slow heartbeat, heart and blood vessel disease,
- Lowering of white blood cells, low sodium levels in the blood, weight loss.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Emvoid

Store below 30°C, Protect from light and moisture.
Keep out of reach of children

9.6 Contents of the pack and other information

Each combipack of EMVOID 125mg/80mg contains:

Aprepitant Capsules I.P. 125 mg (1 Capsule)

Aprepitant Capsules I.P. 80 mg (2 Capsules)

The excipients used are Mannitol, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Hydroxy propyl cellulose, Purified Water and Approved colours used in capsule shell.

10 Details of manufacturer

Manufactured by:
MSN Laboratories Private Limited (Formulations Division)
Plot No. 42, ANRICH Industrial Estate, Bollaram, Sangareddy District – 502325, Telangana, India.

11. Details of permission or licence number with date

Mfg Lic No. 38/MD/AP/2007/F/CC issued on 07.05.2019

12. Date of revision

Not Applicable

MARKETED BY



TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/ Emvoid 125mg, 80mg /NOV-19/01/PI