1, NAME OF THE MEDICINAL PRODUCT
inApitant Aprepitant 80mg hard capsules
inApitant Aprepitant 125mg 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 125 mg capsule contains 125 mg of sucrose and 0,00026 mmol (0,006 mg) of sodium.
Each 80 mg capsule contains 80 mg of sucrose and 0,00022 mmol (0,005 mg) of sodium.
For the full list of excipients, see section 6.1.
3, PHARMACEUTICAL FORM
Hard capsule.
The 125 mg hard capsules are presented as opaque hard gelatin No 1 capsules with a pink cap and white body, printed with "125mg" on the body with black ink.
The 80 mg hard capsules are presented as opaque hard gelatin No 2 capsules with a white cap and white body, printed with "80mg" on the body with black ink.
4, CLINICAL PARTICULARS
4.1 Therapeutic indications
INAPITANT, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:
- Highly emetogenic cancer chemotherapy, including high-dose cisplatin
- Moderately emetogenic cancer chemotherapy

4.2 Posology and method of administration
INAPITANT is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose of INAPITANT is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3. The package insert for the co-administered 5-HT3 antagonist must be consulted prior to initiation of treatment with INAPITANT.
Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3	Day 4
INAPITANT	**125 mg**	**80 mg**	**80 mg**	**none**
Dexamethasone**	**12 mg orally**	**8 mg orally**	**8 mg orally**	**8 mg orally**
5-HT$_3$ antagonist	**See the package insert for the selected 5-HT$_3$ antagonist for appropriate dosing information.**	none	none	none

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4.
The dose of dexamethasone accounts for drug interactions.
Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3
INAPITANT	**125 mg**	**80 mg**	**80 mg**
Dexamethasone**	**12 mg orally**	none	none
5-HT$_3$ antagonist	**See the package insert 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 drug interactions.
See 4.5 for additional information on the administration of INAPITANT with corticosteroids.
Refer to the full prescribing information for co-administered antiemetic agents.
INAPITANT may be taken with or without food.
No dosage adjustment is necessary based on age, gender, race or Body Mass Index (BMI).
No dosage adjustment is necessary for patients with severe renal insufficiency (creatinine clearance <30 mL/min) or for patients with end stage renal disease undergoing hemodialysis.
No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).
4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Co-administration with pimozide, 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. INAPITANT should be used with caution in these patients (see section 5.2).
CYP3A4 interactions
INAPITANT 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 INAPITANT and for 14 days following each 3-day course of INAPITANT (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 INAPITANT. Alternative non-hormonal back-up methods of contraception should be used during treatment with INAPITANT and for 2 months following the last dose of INAPITANT (see section 4.5).
Excipients
INAPITANT capsules contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
INAPITANT capsules contain sodium. This medicinal product 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 is a substrate, a moderate inhibitor and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with INAPITANT, CYP3A4 is inhibited. After the end of treatment, aprepitant cause 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 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 INAPITANT. the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. INAPITANT 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 INAPITANT and orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, dergotamine, 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 INAPITANT. 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 INAPITANT. 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 1.34-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
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 maybe 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 INAPITANT.
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 INAPITANT.
Aprepitant increased the AUC of midazolam, a sensitive CYP3A4 substrate, 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of 2 mg midazolam was co-administered on Days 1 and 5 of a regimen of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 to 5.
Induction
As a mild inducer of CYP2C9, CYP3A4 and glucuronidation, aprepitant can decrease plasma concentrations of substrates eliminated by these routes within two weeks following initiation of treatment. This effect may become apparent only after the end of a 3-day treatment with INAPITANT. For CYP2C9 and CYP3A substrates the induction is transient with a maximum effect reached after 5-5 days after the end of the INAPITANT 3-day treatment. The effect is maintained for a few days, there after slowly declines and is clinically insignificant by two weeks after the end of INAPITANT 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 INAPITANT and for 2 weeks following each 3-day course of INAPITANT for chemotherapy-induced nausea and vomiting (see section 4.4).
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 INAPITANT. Alternative non-hormonal back-up methods of contraception should be used during treatment with INAPITANT and for 2 months following the last dose of INAPITANT.
5-HT3 antagonists
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 INAPITANT 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 in several-fold increased plasma concentrations of aprepitant (see section 4.4).
Concomitant administration of INAPITANT 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 INAPITANT.
Concomitant administration of INAPITANT with herbal preparations containing St. John's Wort (Hypericumperforatum) 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-fols.
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 Pregnancy and lactation
Contraception in males and females
The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of INAPITANT. Alternative non-hormonal back-up methods of contraception should be used during treatment with INAPITANT and for 2 months following the last dose of INAPITANT (see sections 4,4 and 4,5).
Pregnancy
The potential for reproductive toxicity of aprepitant has not been fully characterized. The potential effects on reproduction of alterations in neurokinin regulation are unknown. INAPITANT should not be used during pregnancy unless clearly necessary.
Breast-feeding
It is not known whether aprepitant is excreted in human milk; therefore, breast-feeding is not recommended during treatment with INAPITANT.
Fertility
The potential for effects of aprepitant on fertility has not been fully characterized.
4,7 Effects on ability to drive and use machines
INAPITANT may have minor influence on the ability to drive, cycle and use machines. Dizziness and fatigue may occur following administration of INAPITANT.
4,8 Side Effects

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

+ Nausea and vomiting were efficacy parameters in the first 5 days of post-chemotherapy treatment and were reported as adverse reactions only thereafter.
4,9 Overdose
In the event of overdose, INAPITANT 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, CLINICAL PHARMACOLOGY
5,1 Pharmacodynamics
Aprepitant is a selective high affinity antagonist at human substance P neurokinin 1 (NK1) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing chemotherapy induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) therapies.
5,2 Pharmacokinetics
Absorption
The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration (Cmax) of aprepitant occurred at approximately 4 hours (Tmax). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.
The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in AUC0-∞ was 26% greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state.
Distribution
Aprepitant is greater than 95% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (Vdss) is approximately 66 L in humans.
Metabolism
Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300 mg dose of 14C-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. Aaprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.
Elimination
Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted.
The apparent plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.
Characteristics in Patients
Gender
No dosage adjustment for aprepitant is necessary based on gender.
Elderly
No dosage adjustment for aprepitant is necessary in elderly patients.
Paediatric
The pharmacokinetics of aprepitant have not been evaluated in patients below 18 years of age.
Race
No dosage adjustment for aprepitant is necessary based on race.
Body Mass Index (BMI)
Body Mass Index (BMI) had no clinically meaningful effect on the pharmacokinetics of aprepitant.
Hepatic insufficiency
Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. No dosage adjustment for aprepitant is necessary in patients with mild to moderate hepatic insufficiency.
There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).
Renal Insufficiency
No dosage adjustment for aprepitant is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing hemodialysis.
6, PHARMACEUTICAL PARTICULARS
6,1 List of excipients
Hypromellose 2910, Poloxamer 407, Purified Water, Sucrose, Cellulose (microcrystalline), Gelatin, Sodium laurilsulfate, Titanium dioxide (E171, CI 77891) and Black Printing Ink
The 125mg capsules also contain Iron oxide Red (E172, CI 77491)
6,2 Shelf-life
Refer to outer carton
6.3 Special precautions for storage
Store below 30°C.
6,4 Nature and contents of container
INAPITANT is packaged as a tri-pack containing 1 capsule of inApitant Aprepitant 125mg hard capsules and 2 capsules of inApitant Aprepitant 80mg hard capsules.
Manufacturer
PHARMATHEN INTERNATIONAL S.A
Industrial Park Sapes
Rodopi Prefecture
Block No 5
Rodopi 69300
Greece
Product Registration Holder
Intega Sdn Bhd
8-08, Level 8, Menara MBMR,
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This Package Insert was last revised in February 2025

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