RISK MANAGEMENT PLAN:

EU QPPV FOR THIS RMP

Active substance(s): Aprepitant

Product(s) concerned: EMEND

MAH / MAA name: Merck Sharp & Dohme B.V.

Waarderweg 39

2031 BN Haarlem

The Netherlands

EU Qualified Person for Pharmacovigilance (QPPV) name:	Guy Demol

DOCUMENT ID: 05NYT0

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)

EU RISK MANAGEMENT PLAN (RMP) FOR

Aprepitant

Hard capsules

And

Powder for Suspension

RMP version to be assessed as part of this application:

RMP Version number: 5.1

Data lock point for this RMP: 25-MAR-2020

Date of final sign off: 21-MAY-2020

Rationale for submitting an updated RMP: The Marketing Authorisation Holder (MAH) has updated the EU RMP (Version 4.1) based on the EMEND Periodic Safety Update Report (PSUR) procedure (PSUSA/00000229/201903) European Medicines Agency Pharmacovigilance Risk Assessment Committee's (PRAC) recommendation to evaluate removal of safety concerns listed within the Important Identified Risks, Important Potential Risks, and Missing Information in accordance with the EU Good Pharmacovigilance Practices (GVP) Module V (Revision 2).

Summary of significant changes in this RMP:

The MAH has made the following changes to the EU RMP (Version 4.1), both reflecting updates to the RMP template and re-evaluation of safety concerns based on the guidance in the EU GVP Module V (Revision 2):

	EU RMP (Version 4.1) Safety Concerns	EU RMP (Version 5.1) Safety Concerns
Important identified risks	• Hypersensitivity • Drug interaction: hormonal contraceptives	None
Important potential risks	• Potential for medication errors	None
Missing information	• Use in pregnancy • Use in patients < 6 months of age or weighing <6kg • Use in patients with moderate or severe hepatic impairment	None

Furthermore, the MAH has:

- Removed information regarding both the 40 mg and 165 mg strength and the postoperative nausea and vomiting (PONV) therapeutic indication
- Updated the post-authorisation exposure in Part II: Module SV with cutoff date of 25-Mar-2020.
- Updated data in Part II: Epidemiology of the Indications and Target Populations

Other RMP versions under evaluation: Not applicable.
Details of the currently approved RMP:

Version number: 4.1

Approved with procedure: EMEA/H/C/0527/X/049/G

Date of approval (opinion date): 22 October 2015

QPPV name: Guy Demol, MD

QPPV signature: see signature page

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CT	Computed Tomography
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
PAES	Post-authorisation Efficacy Study
PASS	Post-authorisation Safety Study
PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once Daily

QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TIW	Three Times Per Week
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or Generic name)**	Aprepitant
Pharmacotherapeutic group(s) (ATC Code)	Antiemetics and antinauseants ATC code: A04AD12
Marketing Authorisation Holder	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Number of medicinal products to which this RMP refers	1 This Risk Management Plan is for aprepitant (MK-0869; EMEND), some information regarding fosaprepitant (MK-0517; IVEMEND) is also included in this RMP. Please refer to the RMP for fosaprepitant for additional details (including exposure data) regarding fosaprepitant.
Invented name(s) in the European Economic Area (EEA)	EMEND®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Morpholine derivative (Neurokinin-1 receptor antagonist)
	Summary of mode of action: Aprepitant is a selective high-affinity antagonist at human substance P neurokinin-1 (NK1) receptors.
	Important information about its composition: Each 125 mg capsule contains 125 mg of aprepitant. Each 80 mg capsule contains 80 mg of aprepitant Each sachet contains 125 mg of aprepitant. After reconstitution, 1 mL oral suspension contains 25 mg of aprepitant
Hyperlink to the Product Information	Refer to Summary of Product Characteristics (SmPC)

Table I.1: Product Overview

Indication(s) in the EEA	Current: Emend 125mg/80mg capsules Prevention nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12. EMEND 125 mg/80 mg is given as part of combination therapy. Emend 125 mg powder for oral suspension Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in children, toddlers and infants from the age of 6 months to less than 12 years. EMEND powder for oral suspension is given as part of combination therapy
	Proposed: Removal of PONV indication: EMEND is indicated in adults for the prevention of postoperative nausea and vomiting.
Dosage in the EEA	Current: **Adults:** 3-Day Regimen The recommended dose of EMEND for the 3-day oral regimen is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3. **Adolescents (aged 12 to 17 years):** The recommended dose of capsules of EMEND is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. **Children (aged 6 months to less than 12 years):** The recommended dose of EMEND for oral suspension is based on weight as specified in the product information.
	Proposed: Removal of dosing information pertaining to deletion of 40 mg and 165 mg dosing

Table I.1: Product Overview

Pharmaceutical form(s) and strengths	Current: Hard capsule: 80 mg, 125 mg, Powder for oral suspension: 125 mg
	Proposed: Removal of 40 mg and 165 mg strengths
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Chemotherapy Induced Nausea and Vomiting

Incidence:

CINV adult population:

There are a few studies estimating the incidence of chemotherapy-induced nausea and vomiting (CINV) in a general cancer patient population; however, there are intrinsic difficulties in these types of studies. The difficulties relate to the variety of chemotherapy drugs, doses and antiemetic agents received by the patients, as well as to their different disease conditions and stages [Ref. 5.4: 03P9JF]. This can make comparisons across studies problematic.

Summarized in **Tables SI.1** and **SI.2** are eleven population-based studies estimating the incidence of nausea and vomiting in the acute (Day 1) and delayed (Days 2-5) phases following highly and moderately emetogenic chemotherapy (HEC and MEC). CINV incidence estimates are provided separately for MEC and HEC in **Table SI.1**, whereas incidence for both HEC and MEC, combined, are presented in **Table SI.2**. The data are from multi-centre studies conducted in Europe, the United States (US), Mexico, Canada, Japan and Taiwan.

Table SI.1: Incidence of CINV in MEC and HEC by Acute and Delayed Phases

Country	Population		Nausea	Vomiting
Denmark **France Germany** **Italy** **UK** **US** [Ref. 5.4: 03QXWF, 03QJJX]	n = 298 HEC: 67 MEC: 231 72% female 49.3% breast cancer Median age: 55.5 years ± 12.2 years (range: 19-87)	**HEC**	**% (n)**	**% (n)**
		Acute	33.3% (21)	11.9% (7)
		Delayed	60.3% (38)	50% (29)
		MEC	**% (n)**	**% (n)**
		Acute	36.6% (83)	13.2% (30)
		Delayed	52.4% (119)	27.9 (63)
Mexico [Ref. 5.4: 03QJKH]	n = 73 HEC: 57 MEC: 16 92% female 60% breast cancer Median age: 50 years ± 14 years (range: 22-78)	**HEC**	**% (n)**	**% (n)**
		Acute	57.9% (33)	52.6% (30)
		Delayed	75.4% (43)	63.2% (36)
		MEC	**% (n)**	**% (n)**
		Acute	31.3% (5)	18.8% (3)
		Delayed	68.8% (11)	43.8% (7)
Taiwan [Ref. 5.4: 03QJKB]	n = 107 HEC: 42 MEC: 65 75.7% female 74% breast cancer Mean age: 49.2 years ± 9.5 years	**HEC**	**% (n)**	**% (n)**
		Acute	43% (18)	21% (9)
		Delayed	64% (27)	60% (25)
		MEC	**% (n)**	**% (n)**
		Acute	55% (36)	18% (12)
		Delayed	74% (48)	55% (36)
US [Ref. 5.4: 03QJK5]	n = 322 73% female 87% White 7% Black 3% Hispanic • Cisplatin (HEC), n=47 [Ref. 5.4: 03Q35H] • Carboplatin (MEC), n=106 [Ref. 5.4: 03Q35H] • Doxorubicin (MEC), n=169 [Ref. 5.4: 03Q35H] 44% breast cancer Mean age: 56.6 years ± 12.7 years (range: 27-91)	**HEC[a]**	**% (n)**	**% (n)**
		Acute	75% (35)	10.6% (5)
		Delayed	75% (35)	34% (16)
		[a]Combined patients who received cisplatin-containing chemotherapy regimens (categorized high emetogenic potential) [Ref. 5.4: 03Q35H]		
		MEC[b]	**% (n)**	**% (n)**
		Acute	76% (210)	11% (31)
		Delayed	72% (199)	24% (65)
		[b]Combined patients who received doxorubicin- or carboplatin-containing chemotherapy regimens (moderate emetogenic potential) [Ref. 5.4: 03Q35H]		
Italy [Ref. 5.4: 03QJJW]	n = 152 61.8% male 46.1% < 60 years 53.9% > 60 years 44.7% non-small-cell lung cancer 55.3% others	**HEC***	**% (n)**	**% (n)**
		Acute	38.2% (58)	15.1% (23)
		Delayed	57.9% (88)	29.6% (45)
		*Cisplatin-containing regimens (high emetogenic potential) [Ref. 5.4: 03Q35H]		
Canada [Ref. 5.4: 03QJJY]	n = 143 97.8% female breast cancer patients 85.6% anthracycline-based chemotherapy (MEC) [Ref. 5.4: 03Q35H] Mean age: 51.4 years (range: 24-76)	**MEC[#]**	**%**	**%**
		Acute	37%	13%
		Delayed	70%	15%
		[#]85.6% of patients received anthracycline chemotherapy (epirubicin or doxorubicin) of moderate emetogenic potential [Ref. 5.4: 03Q35H]		
Spain [Ref. 5.4: 050L46]	n = 240 44.2% female 47.5% colorectal cancer MEC: 100% Mean age: 64.4 years ± 10.6	**MEC[a]**	**% (n)**	**% (n)**
		Acute	23.3% (42)	9.2% (17)
		Delayed	38.5% (89)	16.5% (38)
		[a] 62.5% received platinum-based chemotherapy regimens		
Japan [Ref. 5.4: 050L48]	n = 190 42.6% female 100% colorectal cancer MEC: 100% Mean age: 63 years (range: 19-82)	**MEC[a]**	**% (n)**	**% (n)**
		Acute	6.8% (13)	2.1% (4)
		Delayed	37.4% (71)	12.6% (24)
		[a] 91.6% received oxaplatin-based chemotherapy regimens		
NR = Not reported, HEC = Highly emetogenic chemotherapy, MEC = Moderately emetogenic chemotherapy				

Table SI.2: Incidence of CINV in MEC and HEC (combined) by Acute and Delayed Phases

Country	Population		Nausea	Vomiting
Spain **Austria Switzerland** **Germany** [Ref. 5.4: 03QJK2]	n = 243 HEC: 76% MEC: 22% 78% female 59% breast cancer Mean age: 54 years ± 11.7 years	**MEC and HEC**		
		Acute	42%	13%
		Delayed	44-52%	38%
Spain [Ref. 5.4: 03QJKC]	n = 77 51.9% female Acute myeloid leukaemia inpatients Mean age: 49.3 years ± 1.8 years	**MEC and HEC***		
		Acute	23.7%	17.1%
		Delayed	55.8%	51.9%
		*Multiple-day moderately to highly emetogenic chemotherapy (Hesketh level 3-5) [Ref. 5.4: 03P6SM]		
US [Ref. 5.4: 03QJJZ]	n = 151 82% non-Hispanic white 10% African-American 6% Hispanic 2% other 82% female 55% breast cancer HEC:68% Mean age: 56 years ± 13 years	**MEC and HEC***		
			%(n)	**%(n)**
		Acute	31% (45)	13% (19)
		Delayed	49% (72)	33% (50)
		*First cycle of chemotherapy, complete data for n = 146		
HEC = Highly emetogenic chemotherapy, MEC = Moderately emetogenic chemotherapy				

CINV pediatric population:

Chemotherapy-induced nausea and vomiting (CINV) are significant problems in pediatric patients receiving chemotherapy.

Two population-based studies on the incidence of CINV were identified. The first study was conducted among 224 patients wherein 1256 surveys were collected between October 1998 and December 2003 [Ref. 5.4: 03QGC2]. Data on the proportion of those who had nausea and/or vomiting by age group, emetogenicity and phase (acute, delayed) are provided in **Tables SI.3** and **SI.4**. Based on these data, uncontrolled acute CINV among pediatric and adolescent patients remains a problem for ~17% to 36% receiving MEC regimens and for as many as 60% of elementary aged children receiving highly or severely emetogenic regimens despite the use of standard antiemetic therapy.

Table SI.3: Rates of CINV by Age and Emetogenic Chemotherapy, Acute Phase

Age group	MEC (%)	HEC (%)
Toddler (birth-3 yrs)	16.9	34.3
Elementary (4-11 yrs)	26.9	60.9
Adolescent (12-20 yrs)	36.1	55.4

Table SI.4: Rates of CINV by Age and Emetogenic Chemotherapy, Delayed Phase

Age group	MEC (%)	HEC (%)
Toddler (birth-3 yrs)	27.4	34.4
Elementary (4-11 yrs)	38.7	56.5
Adolescent (12-20 yrs)	29.2	53.6

The second study was a prospective observational study evaluating delayed vomiting in 82 evaluable cancer patients, ages 1 to 21 years, exposed to highly or moderately emetogenic chemotherapy agents [Ref. 5.4: 04PLL0]. Vomiting in the acute phase occurred in 24% of these patients, while delayed vomiting occurred in 32% of patients.

Prevalence: No Data Available

Demographics of the population in the authorised indication and risk factors for the disease:

CINV adult population:

CINV may occur in patients of any age, race or gender receiving cancer therapy. It is notable that there is a higher percentage of female to male patients in most population-based studies. The reason may be the predominance of breast cancer diagnosis at the cancer centres where these studies were conducted. Among the patient-related risk factors for CINV is the female gender and younger patient (age < 50 years) [Ref. 5.4: 03QNKB, 03QGC6, 03QNLM]; however, the condition may occur in any patient age group receiving chemotherapy. No data are available reporting the incidence of CINV by age, gender or ethnicity/race. **Table SI.5** was created using the current treatment guidelines from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for 5 of the top 10 cancers by site diagnosed in the US [Ref. 5.4: 03QNLN]. The highly or moderately emetogenic chemotherapeutic agents that may be used for treatment of these cancer types are reported.

Table SI.5: Chemotherapy Treatments[a] for Five Cancer Types by Degree of Emetogenicity

Cancer type	Chemotherapeutic agent	Degree of emetogenicity [Ref. 5.4: 03Q35H]
Breast cancer [Ref. 5.4: 03QJXS]	Cyclophosphamide[b]	High or moderate
	Doxorubicin	Moderate
	Epirubicin	Moderate
	CMF (cyclophosphamide, methotrexate and 5-FU)	High or moderate/low
	CAF (cyclophosphamide, doxorubicin and 5-FU)	High or moderate/low
	CEF (cyclophosphamide, epirubicin and 5-FU)	High or moderate/moderate/low
	EC (epirubicin and cyclophosphamide)	Moderate/high or low
	AC (doxorubicin and cyclophosphamide)	Moderate/high or moderate
	TAC (docetaxel, doxorubicin and cyclophosphamide)	Low/moderate/high or moderate
	AC followed by T (doxorubicin and cyclophosphamide, followed by paclitaxel)	Moderate/high or moderate/low
	TC (docetaxel and cyclophosphamide)	Low/high or moderate
	AT (doxorubicin and docetaxel; doxorubicin and paclitaxel)	Moderate/low
Melanoma of the skin [Ref. 5.4: 03QJXT]	Dacarbazine	High
	Carboplatin	Moderate
	Cisplatin	High
Colorectal [Ref. 5.4: 03QJXV, 03QJXW]	Irinotecan	Moderate
	Oxaliplatin	Moderate
	Irinotecan alone	Moderate
	Capecitabine with either irinotecan or oxaliplatin	Low/moderate/moderate
Non Hodgkin lymphoma [Ref. 5.4: 03QJXX]	Cyclophosphamide	High/moderate
	Doxorubicin	Moderate
Urinary bladder [Ref. 5.4: 03QJXY]	Doxorubicin	Moderate
	IV: MVAC: • Methotrexate • Vinblastine • Doxorubicin • Cisplatin	 Low Minimal Moderate High

[a] Chemotherapeutic agents with the highest emetogenic potential for the selected cancers.
[b] Cyclophosphamide classified as high or low emetogenicity depending on the dosage (high: ≥1500 mg/m^2; moderate: <1500 mg/m^2)

The risk of CINV varies based on the type of treatment received, as well as several other factors. Some types of chemotherapy are more prone to causing nausea and vomiting than others. Some chemotherapeutic agents may not cause nausea and vomiting on their own, but when used in combination with other agents, they can cause nausea. Regimens that are linked to a high incidence of nausea and vomiting are referred to as highly emetogenic chemotherapy' (HEC), and those causing a moderate incidence of nausea and vomiting are referred to as 'moderately emetogenic chemotherapy' (MEC). In addition to the type of treatment, other factors include female gender and younger age.

CINV pediatric population:

Little information exists on risk factors and the demographic profile of pediatric patients experiencing CINV. In one US-based study, lower rates of CINV were reported in toddlers (birth to 3 yrs) relative to elementary and adolescent (4 to 20 yrs) patients [Ref. 5.4: 03QGC2]. The difference in rates has been hypothesized to be related to higher endogenous cortisol production, lower anxiety and possibly lower perception of nausea/vomiting among younger children. In a second US-based study, a history of motion sickness and increased number of chemotherapy cycles was shown to increase the risk of delayed vomiting [Ref. 5.4: 04PLL0]. As with adults, the emetogenicity of the chemotherapy is the single most important risk factor for CINV among children for both studies.

The main existing treatment options: The standard treatment for prevention of acute nausea and vomiting in patients treated with HEC or MEC (containing doxorubicin or epirubicin in combination with cyclophosphamide) is a three-medicine regimen of dexamethasone, a 5-HT3 receptor antagonist (such as ondansetron and granisetron) and aprepitant (either in the form of fosaprepitant injected through a vein or aprepitant given orally).

For preventing delayed nausea and vomiting in patients treated with HEC, a two-medicine

regimen of dexamethasone and aprepitant is the standard. For MEC containing doxorubicin or epirubicin in combination with cyclophosphamide, the standard treatment for delayed nausea and vomiting is aprepitant.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Potential health risks from uncontrolled CINV in both adult and pediatric patients include impaired nutritional intake, electrolyte imbalances, and pulmonary and gastrointestinal complications such as aspiration pneumonia [Ref. 5.4: 03P9JF]. In addition, uncontrolled CINV can result in patient non-compliance with a chemotherapy regimen or a delay or cessation of an effective course of therapy.

Important co-morbidities:

The data available to describe the prevalence of comorbidities in adult patients receiving HEC and MEC regimens are from the control arms (Standard Regimen) of clinical studies supporting aprepitant (the oral formulation) for the prevention of CINV in adults: Protocol 052, Protocol 054 and Protocol 071). The common comorbidities observed during clinical studies of adults for prevention of CINV (Protocols 052, 054 and 071) included hypertension, cough, drug allergy, chronic obstructive pulmonary disease, diabetes mellitus, gastritis, insomnia, depression, and anxiety. The data available to describe the prevalence of comorbidities in pediatric patients receiving emetogenic chemotherapy regimens are from the control arms (Standard Regimen) in clinical studies supporting aprepitant (the oral formulation) for the prevention of CINV: Protocol 097, Protocol 134 and Protocol 208.

Common comorbidities seen in paediatric clinical studies for the prevention of CINV (Protocols 097, 134, 208) are anemia, thrombocytopenia, neutropenia, nausea, vomiting, constipation and infections.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Aprepitant has been extensively evaluated in a series of oral toxicity studies in rodent and non-rodent animal species to determine its safety profile. Fosaprepitant, the water-soluble phosphoryl pro-drug of aprepitant, is rapidly converted to aprepitant *in vivo* following intravenous administration. The pharmacologic activity of fosaprepitant is derived from aprepitant. Toxicity studies were also conducted with intravenous administration of fosaprepitant. The oral and intravenous studies were designed to elicit toxicity and/or to maximize systemic exposure to the active moiety aprepitant.

Outline of Safety Concerns That Have Not Been Adequately Addressed by Clinical Data or Which are of Unknown Significance

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Liver toxicity Aprepitant and fosaprepitant have been shown to induce hepatic cytochrome P-450 (CYP-450) enzymes in rodents. The principal findings observed in the liver (increased liver weights and centrilobular hepatocellular hypertrophy), thyroid (increased thyroid weights and thyroid follicular cell hyperplasia), and/or pituitary (pituitary cell vacuolation) in the rodent studies up to 1 year in duration were anticipated and were consistent with changes reported for structurally and pharmacologically dissimilar compounds that have been shown to induce hepatic P-450 enzymes. In the oral 2-year carcinogenicity studies in rats with aprepitant, the increased incidence of hepatocellular adenomas and carcinomas and thyroid follicular cell adenomas and carcinomas were a consequence of the constellation of changes associated with hepatic enzyme induction. Likewise, the hepatocellular adenomas and carcinomas in the oral 2-year mouse carcinogenicity studies with aprepitant were associated with hepatic enzyme induction. Plasma systemic exposures to aprepitant at these doses were up to 2-fold* (3-fold**) of the human therapeutic exposure. In an oral chronic dog study with aprepitant, the only change noted in the liver was a slight increase in weight with no gross or histologic correlate. This change was noted at a dose where the systemic exposure to aprepitant was 40-fold* (70-fold**) in excess of the therapeutic exposure. At the no-effect level, the plasma systemic exposure to aprepitant was 30-fold* (50-fold**) in excess of the therapeutic exposure.	**Liver toxicity** These findings in the rodent studies are well documented to be rodent-specific adaptive changes associated with hepatic enzyme induction and are of minimal toxicological significance to human risk assessment. The tumour promotion phenomenon observed in rodents caused by hepatic P-450 enzyme induction has not been shown to occur in humans.
Reproductive toxicity In repeated-dose oral toxicity studies in dogs with aprepitant, testicular degeneration and prostatic atrophy were observed in the presence of significantly decreased body weight gain at plasma systemic exposures to aprepitant 20-fold* (30-fold**) the therapeutic exposure. Plasma systemic exposure at the no-effect level provided an 8-fold* (13-fold**) safety margin.	**Reproductive toxicity** The relevance to humans of the findings in the testes and prostate observed at plasma aprepitant systemic exposures twenty-fold* the therapeutic exposure is considered to be low.
In a repeated dose oral juvenile toxicity study in rats with aprepitant, slight changes in the onset of sexual maturation were observed in female and male rats (accelerated vaginal patency and delayed preputial separation up to 4 days compared to control). By the last observation day, all but one male rat in each of the control and drug-treated groups achieved criterion. There were no subsequent effects on mating performance, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. Plasma aprepitant exposures were equivalent to or less than the therapeutic exposure in pediatric patients**	The relevance to humans of the slight changes in the onset of sexual maturation observed at plasma aprepitant systemic exposures equivalent or less than the therapeutic exposure in pediatric patients** is considered to be minimal due to the lack of subsequent effects on reproductive function or histomorphology.
* Exposure multiples calculated based on adult human plasma aprepitant exposure observed with 165 mg oral aprepitant. ** Exposure multiples calculated based on adult human plasma aprepitant exposure observed with 125/80/80 mg aprepitant and in pediatric patients 6 months to <12 years of age.	

Need for Additional Nonclinical Data for Use in Special Populations

An oral juvenile toxicity study in rats was conducted with aprepitant to support use of the drug in pediatric patients. No additional non-clinical studies have been conducted to support the use of aprepitant in other special populations.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Aprepitant (EMEND, MK-0869 and formerly L-754030) is a potent and selective substance P (NK1-receptor) antagonist, that given in combination with other antiemetic agents, has received marketing approval for use in adults in the United States, European Union and in over 80 countries for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic and moderately emetogenic cancer chemotherapy (HEC and MEC, respectively). The currently approved 3-day dosing regimen for orally administered aprepitant (for both HEC and MEC) is 125 mg on Day 1 followed by 80 mg on Days 2 and 3. Single day regimens of 165mg and 40 mg of oral aprepitant, for the prevention of CINV and PONV respectively, were previously developed and registered in some countries. The clinical trial exposure data as follows encompasses all current and previously approved regimens.

The safety profile of the approved oral aprepitant regimen has be evaluated in clinical studies including approximately 6475 adults.

Aprepitant has received marketing approval in the United States and European Union for use in pediatrics (6 months to 17 years of age) for the prevention of chemotherapy induced nausea and vomiting (CINV). For pediatric patients 12 years of age and older, the approved 3-day oral dosing regimen is the same as for adults (125mg on Day 1 and 80mg on Days 2-3). For pediatric patients six months to less than 12 years of age, the approved weight-based dose of an aprepitant powder for suspension (PFS) is 3mg/kg on Day 1 followed by 2mg/kg on Days 2 and 3.

There have been 5 completed clinical trials in the aprepitant pediatric development program; 3 for CINV (Protocols 097, 134 and 208) and 2 for PONV (Protocols 148 and 219) in which approximately 500 subjects were exposed to aprepitant.

The exposure to aprepitant by duration, dose, age group and gender, and ethnic origin is presented in **Tables SIII.1** through **Table SIII.20**. These tables represent the study populations in which the drug has been approved in adults for use including CINV in and PONV. These tables also include exposures from the pediatric population studied for CINV and PONV. Exposures are also displayed from adults with depression administered aprepitant at doses up to 375 mg/day for up to 8 weeks.

Duration of Exposure

Table SIII.1: Clinical Trial Exposure to Aprepitant by Duration of Exposure (Totals for Adult CINV HEC [Aprepitant Protocols 007, 012, 40/42, 052, 054 and 801, and Fosaprepitant Protocol 017L1] and adult CINV MEC [Aprepitant Protocols 044, 071 and 130])

Minimum exposure	Persons	Person-time (in years)
1 day	77	0.2
2 days	23	0.1
3 days	1714	14.1
4 days	16	0.2
>4 days	1807	45.3
Each person is counted once on each applicable duration category row		

Table SIII.2: Clinical Trial Exposure to Aprepitant (Capsule Formulation) by Duration of Exposure for Adolescent Patients (12 to 17 Years of Age) (Totals for Protocols 097 and 208 Pediatric CINV Studies)

Minimum exposure	Persons	Person time (in years)
1 to 3 days	40	0.3
4 to 6 days	23	0.4
7 to 9 days	21	0.5
10 to 12 days	18	0.6
13 to 15 days	9	0.4
16 to 18 days	9	0.4
19 to 24 days	2	0.1
25 to 30 days	1	0.1

Table SIII.3: Clinical Trial Exposure to Aprepitant (PFS Formulation) by Duration of Exposure (Totals for Protocols 148, 208 (6 mos. to <12 Years of Age), P134 (Parts IA, II, and IV), and 219)

Minimum exposure	Persons	Person time (in years)
1 to 3 days	370	1.5
4 to 6 days	27	0.4
7 to 9 days	20	0.5
10 to 12 days	12	0.4
13 to 15 days	28	1.1
16 to 18 days	17	0.8
One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.		

Table SIII.4: Clinical Trial Exposure to Aprepitant (All Formulations) by Duration of Exposure (Totals for Protocols 097, 134 (Parts IA, II and IV), 148, 208 and 219)

Minimum exposure	Persons	Person time (in years)
1 to 3 days	410	1.8
4 to 6 days	50	0.8
7 to 9 days	41	1.0
10 to 12 days	30	1.0
13 to 15 days	37	1.5
16 to 18 days	26	1.3
19 to 24 days	2	0.1
25 to 30 days	1	0.1
One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.		

Table SIII.5: Clinical Trial Exposure to Aprepitant by Duration of Exposure (Totals for Protocols 008, 020, 028, and 039-Depression Studies)

Minimum exposure	**Persons**	**Person-time (in years)**
≤1 week (1 to 7 days)	81	0.7
2 weeks (8 to 14 days)	58	1.8
3 weeks (15 to 21 days)	39	1.8
4 weeks (22 to 28 days)	42	3
>4 weeks (>29 days)	723	131.4

Age Group and Gender

Table SIII.6: Clinical Trial Exposure to Aprepitant by Age Group and Gender (Totals for Adult CINV HEC [Aprepitant Protocols 007, 012, 40/42, 052, 054 and 801, and Fosaprepitant Protocol 017L1] and Adult CINV MEC [Aprepitant Protocols 044, 071 and 130])

Age group (years)	**Persons**		**Person-time (in years)**	
	Male	Female	Male	Female
<18	0	4	0	0.1
18-64	1474	1191	27.9	16.6
≥65	407	545	7.4	7.6

Table SIII.7: Clinical Trial Exposure to Aprepitant (Capsule Formulation) by Age Group and Gender for Adolescent Patients (12 to 17 Years of Age) (Totals for Protocols 097 and 208 Pediatric CINV Studies)

Age group	Persons		Person time (in years)	
	Male	Female	Male	Female
6 years to < 12 year	.	1	.	0.0
12 to 17 years	64	56	1.5	1.2
18 years to 19 years	2	.	0.1	.

Table SIII.8: Clinical Trial Exposure to Aprepitant (PFS Formulation) by Age Group and Gender (Totals for Protocols 148, 208 (6 mos. to <12 years of age), P134 (Parts IA, II, and IV), and 219)

Age group	Persons		Person time (in years)	
	Male	Female	Male	Female
birth to <2 years	70	40	0.6	0.3
2 to <6 years	80	65	1.0	0.7
6 to <12 years	90	57	1.2	0.6
12 to 17 years	38	34	0.1	0.1
Only P219 included subjects < 6 months of age. One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.				

Table SIII.9: Clinical Trial Exposure to Aprepitant (All Formulations) by Age Group and Gender (Totals for Protocols 097, 134 (Parts IA, II and IV), 148, 208 and 219)

Age group	Persons		Person time (in years)	
	Male	Female	Male	Female
birth to <2 years	70	40	0.6	0.3
2 to <6 years	80	65	1.0	0.7
6 to <12 years	90	58	1.2	0.6
12 to 17 years	102	90	1.7	1.3
18 to 19 years	2	.	0.1	.
Only P219 included subjects < 6 months of age. One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.				

Table SIII.10: Clinical Trial Exposure to Aprepitant by Age Group and Gender (Totals for Protocols 008, 020, 028 and 039 - Depression Studies)

Age group (years)	**Persons**		**Person-time (in years)**	
	Male	Female	Male	Female
18-64	366	564	49.8	86.9
≥65	6	7	1.1	0.9

Dose

Table SIII.11: Clinical Trial Exposure to Aprepitant by Dose (Totals for Adult CINV HEC [Aprepitant Protocols 007, 012, 40/42, 052, 054 and 801, and Fosaprepitant Protocol 017L1] and Adult CINV MEC [Aprepitant Protocols 044, 071 and 130])

Dose of exposure	Persons	Person-time (in years)
25 mg	120	1.3
40 mg	120	0.3
80 mg	3075	35.8
125 mg	3097	16
160 mg	12	0.0
250 mg	40	1.3
300 mg	311	3.3
375 mg	36	0.3
400 mg	361	1.2
>400 mg	1	0.0
Each person is counted once on each applicable duration category row.		

Table SIII.12: Clinical Trial Exposure to Aprepitant (Capsule Formulation) by Dose For Adolescent Patients (12 to 17 Years of Age) (Totals for Protocols 097 and 208 Pediatric CINV Studies)

Dose of exposure	Persons	Person time (in years)
Any dose	123	2.8
65.1 to 80.0 mg	122	1.9
80.1 to 125 mg	123	0.9
> 125 mg	1	0.0

Table SIII.13: Clinical Trial Exposure to Aprepitant (PFS Formulation) by Dose (Totals for Protocols 148, 208 (6 mos. to <12 Years of age), P134 (Parts IA, II, and IV), and 219)

Dose of exposure	Persons	Person time (in years)
Any dose	474	4.8
< 10.1 mg	60	0.2
10.1 to 20.0 mg	63	0.4
20.1 to 30.0 mg	120	1.0
30.1 to 40.0 mg	161	0.9
40.1 to 50.0 mg	68	0.7
50.1 to 65.0 mg	79	0.7
65.1 to 80.0 mg	66	0.5
80.1 to 125 mg	78	0.4
> 125 mg	2	0.0
One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.		

Table SIII.14: Clinical Trial Exposure to Aprepitant (All Formulations) by Dose (Totals for Protocols 097, 134 (Parts IA, II and IV), 148, 208 and 219)

Dose of exposure	Persons	Person time (in years)
Any dose	597	7.6
< 10.1 mg	60	0.2
10.1 to 20.0 mg	63	0.4
20.1 to 30.0 mg	120	1.0
30.1 to 40.0 mg	161	0.9
40.1 to 50.0 mg	68	0.7
50.1 to 65.0 mg	80	0.7
65.1 to 80.0 mg	189	2.4
80.1 to 125 mg	201	1.3
> 125 mg	1	0.0
One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.		

Table SIII.15: Clinical Trial Exposure to Aprepitant by Dose (Totals for Protocols 008, 020, 028 and 039 - Depression Studies)

Dose of exposure	Persons	Person-time (in years)
10 mg	135	25.5
20 mg	3	0.0†
30 mg	133	24.1
60 mg	4	0.0†
100 mg	133	22.8
125 mg	8	0.0†
200 mg	163	15.0
250 mg	101	10.7
300 mg	205	30.0
375 mg	89	10.3
400 mg	2	0.0†
500 mg	12	0.0†
600 mg	5	0.0†
750 mg	10	0.0†
†cPerson-time is >0 but <0.1.		

Ethnic Origin

Table SIII.16: Clinical Trial Exposure to Aprepitant by Race (Totals for Adult CINV HEC [Aprepitant Protocols 007, 012, 40/42, 052, 054 and 801, Protocol 017L1] and Adult CINV MEC [Aprepitant Protocols 044, 071 and 130])

Race	Persons	Person-time (in years)
Asian	459	5
Black	159	2.9
European	3	0.1
Hispanic American	237	4.6
Multiracial	448	8.2
Native American	51	0.5
Native Hawaiian or Other Pacific Islander	4	0
Polynesian	2	0
White	2258	38.2

Table SIII.17: Clinical Trial Exposure to Aprepitant (Capsule Formulation) by Ethnic Origin and Gender for Adolescent Patients (12 to 17 Years of age) (Totals for Protocols 097 and 208 Pediatric CINV Studies)

Race	Persons	Person time (in years)
American Indian Or Alaska Native	3	0.0
Asian	12	0.4
Black Or African American	8	0.2
Hispanic American	11	0.4
Multiple	12	0.3
White	77	1.6

Table SIII.18: Clinical trial exposure to aprepitant (PFS Formulation) by Race (Totals for Protocols 148, 208 (6 mos. to <12 years of age), P134 (Parts IA, II, and IV), and 219)

Race	Persons	Person time (in years)
American Indian Or Alaska Native	4	0.0
Asian	15	0.5
Black Or African American	10	0.1
Multi-Racial	37	0.2
Multiple	25	0.4
Native Hawaiian Or Other Pacific Islander	1	0.0
White	382	3.6
One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.		

Table SIII.19: Clinical Trial Exposure to Aprepitant (All Formulations) by Race (Totals for Protocols 097, 134 (Parts IA, II and IV), 148, 208 and 219)

Race	Persons	Person time (in years)
American Indian Or Alaska Native	7	0.0
Asian	27	0.9
Black Or African American	18	0.3
Hispanic American	11	0.4
Multi-Racial	37	0.2
Multiple	37	0.7
Native Hawaiian Or Other Pacific Islander	1	0.0
White	459	5.2
One subject from P219 was excluded from this table after being accidentally randomized in IVRS to the 2.5 mg dose arm, which was not evaluated in this study.		

Table SIII.20: Clinical Trial Exposure to Aprepitant By Ethnic Origin (Totals for Protocols 008, 020, 028 and 039 - Depression Studies)

Ethnic origin	Persons	Person-time (in years)
White	747	112.7
Black	101	12.6
Asian	23	2.7
Hispanic American	52	6.8
Multiracial	1	0.0†
European	4	0.7
Native American	9	1.9
Indian	6	1.2

† Person-time is >0 but <0.1.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
General			
Adults previously treated or concomitantly treated with multiple-day therapy with HEC or MEC prior to study initiation	To avoid the potentially confounding effect of prior exposure to emetogenic chemotherapy) and standardize emetic stimulus.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis
Population hypersensitive to ondansetron or dexamethasone	Aprepitant should be administered in conjunction with a corticosteroid (dexamethasone) and a 5-HT3 antagonist (ondansetron). Therefore, this population cannot be treated with simultaneous therapy of Aprepitant + ondansetron + dexamethasone because expected allergic reactions to ondansetron or dexamethasone may lead to serious and/or life-threatening events.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis
Patient has ever participated in a study with aprepitant, or has taken a non-approved (investigational drug) within the last 4 weeks	This exclusion criterion aims to minimise data variability, reduce potential drug interactions, and improve efficiencies of the study logistics.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis
Adult patients with a Karnofsky score <60	Patient's whose functional impairment is greatly reduced may not be able to maintain compliance with study drug compliance and procedures.	No	These patients may benefit from this therapy and the treating Physician will need to make an assessment of the benefit risk per patient basis
Pediatric patients (<10 years of age) with Lansky score ≤60	Administering the study drug to such patients might confound the ability to define the benefit risk profile for aprepitant. Patient impairment may also impact their ability to comply with study procedures.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patients previously treated or is planned to be treated with radiation therapy to abdomen or pelvis within 1 week prior to study initiation or following Study Day 1	Administering the study drug to such patients might confound the results or have an impact on the efficacy of the study drug as radiation therapy to the abdomen and pelvis may alter the threshold for nausea and vomiting.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patients who had vomited and/or had dry heaves/retching within 24 hours prior to the start of chemotherapy on Study Day 1.	Administering the study drug to such patients might confound the results or have an impact on the efficacy of study drug in patients with a high risk of vomiting spontaneously.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis
Concurrent Conditions			
Patient who were mentally incapacitated or had a significant emotional or psychiatric disorder	Mentally incapacitated patients or patients with a significant emotional or psychiatric disorder may have a higher likelihood of poor adherence with study procedures or may interfere with study objectives.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patients who had a serum creatinine >1.5 x the upper limit of normal (ULN) for age	Administering the study drug to such patients might confound the ability to define the benefit risk profile for aprepitant in patients at risk for abnormal creatinine levels (due to underlying disease, chemotherapy, etc).	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patients with severe hepatic impairment AST >2 x ULN (upper limit of normal) (adults) - 5.0 x ULN (pediatrics) ALT >2 x ULN (adults) - >5.0 x ULN (pediatrics) Bilirubin >1.5 x ULN Creatinine > 1.5 x ULN	No dose adjustment is necessary for patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment. Aprepitant should be used with caution in these patients.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patient with abnormal laboratory values: Absolute Neutrophil Count (<1000 to <1500 mm^3 Platelet Count (<100,000/mm^3)	Administering the study drug to such patients might confound the ability to define the benefit risk profile for aprepitant in patients at risk for abnormal counts (due to underlying disease, chemotherapy, etc).	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patient has symptomatic primary or metastatic CNS malignancy.	Administering the study drug to such patients might confound the results of the study as CNS tumors can cause nausea and vomiting.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patient was to receive stem cell rescue therapy in conjunction with course of emetogenic chemotherapy.	Administering the study drug to such patients might confound the results of the study as stem cell rescue therapy is associated with significant nausea and vomiting.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patient has an active infection (e.g. pneumonia), congestive heart failure, bradyarrhythmias, or any uncontrolled disease (e.g. diabetic ketoacidosis, gastrointestinal obstruction) except for malignancy.	Administering the study drug to such patients might confound the ability to define the benefit risk profile for aprepitant in patients with underlying disease that may be unrelated to the malignancy.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Patient currently uses any illicit drugs, including marijuana, or has current evidence of alcohol abuse as determined by the investigator.	Administering the study drug to such patients might confound the results of the study.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis.
Pregnancy and lactation	For aprepitant, no clinical data on exposed pregnancies are available. It is not known whether aprepitant is excreted in human milk. Caution is advised to the patients who are not planning for child, as 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 1 month following administration of aprepitant.	No	Aprepitant should not be used during pregnancy unless clearly necessary. Also, breastfeeding is not recommended during treatment with aprepitant.
Concomitant Medications			
Patients treated with anti-emetic agents 72 hours prior to study initiation (such as 5-HT3 antagonists, phenothiazines, butyrophenones, domperidone, and cannabinoids)	To avoid potentially confounding effect of concurrent administration of antiemetics.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis
Patient has used benzodiazepines or opiates, except for single daily doses of triazolam, temazepam or midazolam, in the 48 hours prior to Treatment Day 1.	To minimise potentially confounding effects of concurrent administration of medications that might alter threshold for emesis and/or nausea.	No	These patients may benefit from this therapy and the treating physician will need to make an assessment of the benefit risk per patient basis

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Population using medicines that are metabolized by CYP3A4	Inhibition of CYP3A4 can result in increased plasma concentrations of the CYP3A4 substrates (e.g. midazolam) when co-administered with a regimen of fosaprepitant followed by aprepitant. Fosaprepitant is rapidly converted to aprepitant, which is a moderate inhibitor of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of the CYP3A4 substrates.	No	As noted in the Contraindications Section, aprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. Aprepitant should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolized through CYP3A4; some chemotherapy agents are metabolized by CYP3A4. Moderate inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products administered orally.
Population using medications that induces CYP3A4 activity (other than those listed as contra-indications) within 30 days of Treatment Day 1	Co-administration of aprepitant with drugs that strongly induce CYP3A4 activity (e.g. rifampin or rifabutin, carbamazepine, barbiturates and St. John's Wort, phenytoin) may result in reduced plasma concentrations and decreased efficacy of aprepitant.	No	Aprepitant, which is a substrate for CYP3A4; therefore, coadministration of aprepitant with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of aprepitant, respectively.
Population using medications that inhibit CYP3A4 within 7 days of Treatment Day 1.	Co-administration of fosaprepitant with strong (e.g. ketoconazole) or moderate (e.g. diltiazem) CYP3A4 inhibitors may result in clinically important elevations of plasma concentrations of fosaprepitant and should be approached with caution. Elevated fosaprepitant concentrations beyond the levels needed to exert its therapeutic effects (i.e. to prevent nausea and vomiting in CINV) could cause unwanted pharmacokinetic interactions with other drugs that may also be concomitantly administered.	No	Aprepitant, which is a substrate for CYP3A4; therefore, coadministration of aprepitant with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of aprepitant, respectively
CINV = Chemotherapy-induced nausea and vomiting, CYP = Cytochrome P, HEC = Highly emetogenic chemotherapy, MEC = Moderately emetogenic chemotherapy			

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table SIV.2.1: Limitations to Detect Adverse Reactions in Clinical Trial Development

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	Aprepitant has been administered to approximately 6475 adults and approximately 500 pediatric subjects in CINV and PONV trials.	This sample size is not enough to allow the detection of rare adverse experiences occurring with a frequency of at least 1 in 10,000.
Due to prolonged exposure	Limited exposure to administration of aprepitant is available; lifetime clinical exposure data does not exist.	Not applicable
Due to cumulative effects	Not applicable	Not applicable
Which have a long latency	Not applicable	Not applicable

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

According to the current product labelling for aprepitant, no dose adjustment is necessary based on age, gender, race or body mass index (BMI). Additionally, no dose adjustment is necessary for patients with renal insufficiency, with end-stage renal disease undergoing haemodialysis or with mild hepatic insufficiency (Child-Pugh score 5 to 6).

Patients with severe hepatic impairment:

There are limited clinical data in patients with moderate hepatic insufficiency (Child-Pugh score 7 to 8) and no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9) for aprepitant or fosaprepitant. Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a clinically relevant extent.

Patients less than 6 months of age or weighing less than 6 kg:

There are limited clinical data in subjects less than 6 months of age or weighing <6 kg in the aprepitant and fosaprepitant pediatric clinical programs; given this lack of experience, dosing in this age group is not recommended.

Pregnancy and Lactation:

There have been no prospective studies evaluating aprepitant or fosaprepitant in pregnant or lactating women. Women of childbearing potential were advised to avoid pregnancy and

were required to use two adequate barrier methods of contraception while participating in clinical studies of aprepitant or fosaprepitant.

During clinical studies, 16 unintended confirmed pregnancies and 1 potential pregnancy were reported in women while exposed to aprepitant (15 patients in the depression program) or fosaprepitant (1 subject in a pharmacokinetic study) [Ref. 5.3.5.4: 03PZGW]. Of those patients, 13 had a positive β-human chorionic gonadotropin (β-hCG) test while exposed to aprepitant and subsequently discontinued the study therapy within 2 weeks. Three patients had a positive β-hCG test documented after more than 14 days of stopping the study therapy and remained off treatment.

The outcomes of the 16 pregnancies were as follows:

- 7 had full-term pregnancies
  - 6 women delivered normal newborns.
  - 1 woman had placenta previa during the sixth month of her pregnancy. In addition, the newborn had a heart murmur, oesophageal reflux, breathing and sinus conditions requiring the use of an apnea monitor, and hydrocele of the [redacted] testicle. The reporting investigator for this patient considered all the events probably not related to the study therapy.
- 5 patients and 1 subject underwent elective abortions, 2 of them resumed the study therapy.
- 2 patients had spontaneous abortions.
- 1 patient had a positive β-hCG test and lost to follow-up.

An additional patient in the depression program had a positive serum β-hCG test, but approximately 6 weeks later reported a negative β-hCG and declined any additional follow-up [Ref. 5.3.5.4: 03PZGW]. The reporting investigator was unable to conclude if the patient was actually pregnant.

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other: Patients < 6 months of age or weighing less than 6kg.	Given the lack of experience in this population, dosing in this age group is not recommended.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure estimates were calculated from our Company's internal distribution data from the Financial Sharing Area database. This data provides a more complete and consistent methodology for the estimate of patient exposure worldwide for current Company products. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.

Aprepitant is given to patients who receive cancer chemotherapy for 3-day cycles (coinciding with chemotherapy cycles) as part of a regimen that includes a corticosteroid and a 5-HT3-receptor antagonist. The recommended dose of aprepitant is either a 125 mg capsule orally 1 hour prior to chemotherapy treatment on Day 1, and an 80 mg capsule once daily in the morning on Days 2 and 3 of chemotherapy treatment, or alternatively, a 165 mg capsule orally on Day 1 only. Since there is wide variation in the number of cycles of chemotherapy administered to any given patient, the estimate of patient exposure to aprepitant for chemotherapy-induced nausea and vomiting is best considered as individual courses of therapy, based on the assumption that one course of therapy consists of either one 125 mg capsule and two 80 mg capsules, or a single 165 mg capsule. Aprepitant powder for suspension is available for pediatric patients 6 months to less than 12 years of age for 3 day cycles. Each single use pouch contains aprepitant 125 mg. The dose is calculated based on the pediatric patient's weight.

Single day regimens of 165mg and 40 mg of oral aprepitant, for the prevention of CINV and PONV respectively, were previously developed and registered in some countries. The post-marketing exposure data presented in **Table SV.1.2.1** encompasses all current and previously approved regimens.

A summary of the worldwide distribution of aprepitant for the cumulative period from market introduction to 25-MAR-2020 is presented in **Table SV.1.2.1** based on the available data. This estimation was based upon the sum of the number of individual 40 mg, 125 mg, and 165 mg capsules, the number of tri-fold packs, and the number of 125 mg powder for suspension single use pouches divided by 3 which were distributed.

SV.1.2 Exposure

The estimated number of doses of aprepitant distributed worldwide from product launch through 25-MAR-2020 is 90,663,791. See **Table SV.1.2.1**.

Table SV.1.2.1: Patient Exposure Worldwide Distribution of Aprepitant Cumulatively to 25-MAR-2020

Strength/Forms distributed	Distribution (total number of doses)
	Cumulative to 25-MAR-2020[a]
40 mg capsules[b]	2,107,677
80 mg capsules[d]	17,860,459
125 mg capsules	8,716,614
Tri-fold pack[c]	79,417,481
165 mg capsules[b]	411,157
Powder for suspension (125 mg) single use pouches	32,585
TOTAL ESTIMATED PATIENT EXPOSURE[d]	**90,663,791**

[a] This estimate of patient exposure for the cumulative reporting period is based on the availability of monthly product distribution figures; hence, this cumulative estimate has been calculated to 29-FEB-2020.

[b] Single day regimens of 165mg and 40 mg of oral aprepitant, for the prevention of CINV and PONV respectively, were previously developed and registered in some countries. The patient exposure encompasses all current and previously approved regimens.

[c] Contains one 125 mg capsule and two 80 mg capsules.

[d] Based on the sum of the number of individual 40 mg, 125 mg, and 165 mg capsules, the number of tri-fold packs, and the number of 125 mg powder for suspension single use pouches divided by 3. The total for 80 mg capsules is excluded from the total estimated patient exposure calculation since this dosage form is given with the 125 mg dose.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Aprepitant is not a drug with known psychotropic or mood-altering effects; therefore, it is highly unlikely that aprepitant would be sought out for illegal use. Thus, no risk minimisation is required.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

In this updated RMP the MAH has removed previously included safety concerns following the European Medicines Agency PRAC's recommendation to evaluate removal of the safety concerns listed within the Important Identified Risk, Important Potential Risk and Missing Information in accordance with EU GVP Module V (Revision 2) guidance (PSUSA/00000229/201903).

Removal of Safety Concerns

Important Identified Risks:

Hypersensitivity

Rationale: Hypersensitivity to aprepitant is currently described within sections 4.3 Contraindications and 4.8 Undesirable Effects of the SmPC for aprepitant. This risk is adequately managed by current routine risk minimisation (labeling) and no need for additional risk minimisation has been identified. The risk is followed through routine pharmacovigilance activities for aprepitant. There is no reasonable expectation that additional pharmacovigilance activity can further characterise the risk. Therefore, hypersensitivity is no longer considered to require inclusion as an important identified risk in the EU RMP for aprepitant.

Drug interaction: hormonal contraceptives

Rationale: Drug interaction with hormonal contraceptives is currently described within sections 4.4 Special Warnings and Precautions for Use, 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction and 4.6 Fertility, Pregnancy and Lactation of the SmPC for aprepitant. This risk is adequately managed by current routine risk minimisation (labeling) and no need for additional risk minimisation has been identified. The risk is followed through routine pharmacovigilance activities for aprepitant. There is no reasonable expectation that additional pharmacovigilance activity can further characterise the risk. Therefore, drug interaction with hormonal contraceptives is no longer considered to require inclusion as an important potential risk in the EU RMP for aprepitant.

Important Potential Risk:

Potential for medication errors

Rationale: The potential for medication errors is currently addressed within Section 4.2 Posology and Method of Administration of the SmPC which adequately describes measures

to prevent the occurrence of medication errors by providing clear written preparation instructions and clear dosage and administration information for aprepitant. This risk is adequately managed by current routine risk minimisation measures (labeling), and no need for additional risk minimisation activities has been identified. The risk is followed through routine pharmacovigilance activities for aprepitant. There is no reasonable expectation that additional pharmacovigilance activity can further characterise the risk. Therefore, potential for medication errors is no longer considered to require inclusion as an important potential risk in the EU RMP for aprepitant.

Missing Information:

Use in pregnancy

Rationale: Review of this missing information indicates that aprepitant use in pregnancy has been monitored via routine pharmacovigilance and managed via routine risk minimisation (labeling). Use in pregnancy is described in the following section of the SmPC: 4.6 Fertility, Pregnancy and Lactation. No need for additional risk minimisation has been identified. No studies are planned to further characterise safety in this population. Therefore, exposure during pregnancy is no longer considered to require inclusion as missing information in the EU RMP for aprepitant.

Use in patients <6 months of age or weighing <6 kg

Rationale: Review of this missing information indicates that aprepitant use in patients less than 6 months of age or weighing less than 6 kg has been monitored via routine pharmacovigilance and managed via routine risk minimisation (labeling). Section 4.1 Therapeutic Indications of the SmPC states that use of aprepitant is approved in patients ages 6 months and older. Clear instruction regarding use of weight to determine dose for patients 6 months to less than 12 years is provided in Section 4.2 Posology and Method of Administration of the SmPC. The pediatric CINV trials were designed to include subjects <6 months of age, but recruitment challenges in this young age group precluded collection of meaningful data to make conclusive determinations with regard to efficacy and safety. Use in patients less than 6 months of age or weighing less than 6 kg is addressed in the following section of the SmPC: 4.2 Posology and Method of Administration. No need for additional risk minimisation has been identified. No studies are planned to further characterise safety in this population. Therefore, use in patients less than 6 months of age or weighing less than 6 kg is no longer considered to require inclusion as missing information in the EU RMP for aprepitant.

Use in patients with moderate or severe hepatic impairment

Rationale: Review of this missing information indicates that aprepitant use in patients with moderate or severe hepatic impairment has been monitored via routine pharmacovigilance and managed via routine risk minimisation (labeling). Use in patients with moderate or severe hepatic impairment is described in the following section of the SmPC: 4.2 Posology and Method of Administration, 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties. No need for additional risk minimisation has been identified. No

studies are planned to further characterise safety in this population. Therefore, use in patients with moderate or severe hepatic impairment is no longer considered to require inclusion as missing information in the EU RMP for aprepitant.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

The Summary of Safety Concerns for aprepitant does not contain any Important Identified Risks or Important Potential Risks.

SVII.3.2 Presentation of the Missing Information

The Summary of Safety Concerns for aprepitant does not contain any safety concerns as Missing Information.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The MAH maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports and PSURs), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labelling and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not applicable.

III.2 Additional Pharmacovigilance Activities

There are no additional risk minimisation measures proposed for aprepitant.

III.3 Summary Table of Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are proposed.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no ongoing or proposed post-authorisation efficacy studies (PAES) for aprepitant.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

The Summary of Safety Concerns for aprepitant does not include any Important Identified Risks, Important Potential Risks or Missing Information. Routine risk minimisation in the form of the product labeling remains in place.

V.2 Additional Risk Minimisation Measures

The Summary of Safety Concerns for aprepitant does not include any Important Identified Risks, Important Potential Risks or Missing Information. Routine risk minimisation measures are sufficient; no additional risk minimisation measures are warranted.

V.3 Summary of Risk Minimisation Measures

The Summary of Safety Concerns for aprepitant does not include any Important Identified Risks, Important Potential Risks or Missing Information. The product labeling effectively minimises product risk.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for EMEND

EMEND's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EMEND should be used.

This summary of the RMP for EMEND should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of EMEND's RMP.

I. The Medicine and What It Is Used For

EMEND, in combination with other antiemetic agents, is authorised for indication in patients 6 months of age and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:

- Highly emetogenic cancer chemotherapy
- Moderately emetogenic cancer chemotherapy

It contains aprepitant as the active substance and is available as 80, 125 capsules and as powder for oral suspension (single-use pouch of 125 mg) for oral administration.

Further information about the evaluation of EMEND's benefits can be found in EMEND's EPAR, including in its plain-language summary, available on the EMA website, at the following link: https://www.ema.europa.eu/en/medicines/human/EPAR/emend

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of EMEND, together with measures to minimise such risks and the proposed studies for learning more about EMEND's risks, are outlined as follows:

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of EMEND's are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EMEND. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

There are no EMEND-specific important identified or potential risks, or missing information that require additional pharmacovigilance or additional risk minimisation activities.

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of aprepitant.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for aprepitant.

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ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.