Division of Gastroenterology and Inborn Error Products

Medical Officer Clinical Review Addendum: NDA 21549/S-025 (b) (4) (b) (4)

NDA Number:	**21549/S-025 (b) (4)**
Established name:	**aprepitant capsule (b) (4) (b) (4)**
Trade Name:	**Emend**
Therapeutic Class:	**NK-1 Receptor Antagonist**
Applicant:	**Merck Sharp & Dohme Corp.**
Intended Population:	**(b) (4)**
Indication:	**Prevention of chemotherapy induced nausea and vomiting**
Clinical Reviewer:	**Karyn L. Berry, MD, MPH**

1. Explanation of Need for Clinical Review Amendment

This document is an addendum to a clinical review completed and finalized in DARRTS on August 17, 2015.

The original clinical review stated that the Applicant adequately demonstrated efficacy of aprepitant for the prevention of chemotherapy induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) in pediatric patients aged (b) (4) . However, outstanding issues related to aprepitant require clarification, including:

- Emetogenic classification scheme used in the key Phase 3 trials (Protocol 208)
- Capsule use in pediatric patients aged less than 12 years, but who weigh at least 30 kg
- Under and overdosing of aprepitant oral suspension in patients aged 6 months to 12 years

These updates to the original clinical review are summarized below with an updated recommendation on regulatory action.

2. Recommendation on Regulatory Action

This reviewer continues to recommend the approval of aprepitant capsules in

patients aged ≥ 12 to 17 years for the prevention of CINV associated with HEC and MEC. Based on pharmacokinetic (PK) data analyzed by the Clinical Pharmacology review team, this reviewer also recommends that aprepitant capsules be approved for use in pediatric patients who are aged <12 and weigh at least 30 kg.

3. Issues to be addressed

a. Emetogenic classification

A schema that appropriately classifies the emetogenic risk of chemotherapy regimens is important to provide a framework for treatment guidelines in the clinical setting and to define and standardize emetogenic potential in clinical trials. For adult CINV trials, a 4-level schema that classifies chemotherapeutic agents by emetogenicity (minimal risk is <10%; low risk is 10% - 30%; moderate risk is 31% - 90% and high risk is >90%) has been used by consensus groups in oncology, including the American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC). See Table 1.

The Applicant stated that this system was developed based on adult experiences and cannot easily be extrapolated to the pediatric population due to potential differences in drug metabolism.

In the key, Phase 3 trial (Protocol 208), the Applicant used a 5-level system proposed by the Children's Oncology Group (COG), that classifies commonly used chemotherapeutic agents by emetogenicity. This classification ranks single chemotherapeutic agents as low risk, mild, moderate, high risk and very high risk, associated with <10%, 10-30%, 30-60%, 60-90% and >90% frequency of causing nausea and vomiting without antiemetic treatment. See Table 2

Table 1: Emesis Risk of Intravenous Antineoplastic Agents (ASCO)

Emetic Risk of Intravenous An ineoplastic Agents

Emetic Risk	Agent
High	Carmustine
	Cispla in
	Cyclophosphamide ≥1,500 mg/m^2
	Dacarbazine
	Dactinomycin
	Mechlorethamine
	Streptozotocin
Moderate	Azacitidine
	Alemtuzumab
	Bendamustine
	Carboplatin
	Clofarabine
	Cyclophosphamide < 1,500 mg/m^2
	Cytarabine > 1,000 mg/m^2
	Daunorubicin*
	Doxorubicin*
	Epirubicin*
	Idarubicin*
	Ifosfamide
	Irinotecan
	Oxaliplatin
Low	Fluorouracil
	Bortezomib
	Cabazitaxel
	Catumaxomab
	Cytarabine ::: 1,000 mg/m^2
	Docetaxel
	Doxorubicin HCL liposome injec ion
	Etoposide
	Gemcitabine
	Ixabepilone
	Methotrexate
	Mitomycin
	Mitoxantrone
	Paclitaxel
	Panitumumab
	Pemetrexed
	Temsirolimus
	Topotecan
	Trastuzumab
Minimal	2-Chlorodeoxyadenosine
	Bevacizumab
	Bleomycin
	Busulfan
	Cetuximab
	Fludarabine
	Pralatrexate
	Rituximab
	Vinblastine
	Vincristine
	Vinorelbine

NOTE. This list of agents is not exhaustive.
Abbreviation: HCL, hydrochloride.
*These anthracyclines, when combined with cyclophosphamide, are now designated as high emetic risk.

Table 2: Emetogenicity of Commonly Used Chemotherapeutic Agents

Adapted from [1] Altman, AJ, ed. *Supportive Care of Children with Cancer*. 3rd ed. Baltimore, MD: The Johns Hopkins University Press; 2004, and [7]Perry MC et al., ed. *Companion Handbook to Chemotherapy Source Book*. 2nd ed. Baltimore, MD: Lippinkott, Williams and Wilkins; 2004.
Added* or revised** from: Antiemetics. National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology- V3.2008. http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf Accessed 5-14-08

Reviewer's comments: During a t-con between the Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Applicant on March 16, 2011, the Applicant questioned the availability of consensus guidelines regarding chemo-therapy emetogenic potential in pediatric patients. Based on minutes from Mr. Jagjit Grewal, former DGIEP Regulatory Project Manager for this product, DGIEP and Pediatric and Maternal Health Staff (now called the Division of Pediatric and Maternal Health) had discussed the most appropriate emetogenic classification system for pediatric patients with the Division of Oncology Products. Reviewers in the oncology division recommended a classification of chemo-therapeutic agents by emetogenic potential for pediatric patients developed by the Children's Oncology Group. This was then conveyed to the Applicant during the above t-con.

In reviewing the two classification systems, there are a number of identified differences such as: dosing levels that qualify an agent for either very high or high emetogenic risk, such as cyclophosphamide > 1500 mg/m^2 (very high risk); ifosfamide ≥1.5 g/m^2 as a very high risk and ifosfamide < 1.5 g/ m^2 as moderate risk in the COG schema, while the ASCO consensus guidelines list cyclophosphamide ≥ 1500 mg/ m^2 as high risk and ifosfamide as moderate risk.

While there are differences between the two schemas, per the Division of Oncology recommendations, the COG emetogenic classification for pediatric patients used by the Applicant in Protocol 208 is acceptable.

b. <u>Aprepitant capsules for patients less than 12 years of age who weigh at least 30 kg.</u>

During the labeling negotiations (b) (4) DGIEP requested that the Clinical Pharmacology Review Team assess whether PK data supported modifying the proposed pediatric dosing for the aprepitant capsule to include pediatric patients aged less than 12 years who weighed at least 30 kg, since the weight based dose for the suspension formulation in this specific pediatric population is equivalent to the adolescent dose.

The Applicant did not conduct a dedicated related bioavailability study (b) (4) The Clinical Pharmacology Reviewer conducted a population PK analyses and found the available PK data supported extending the dosing capsule formulation in children less than 12 years of age who weigh at least 30 kg. See the Clinical Pharmacology Team review addendum in DARRTS.

Reviewer's comments: Use of aprepitant capsule in the patient population who are less than 12 years of age and weigh at least 30 kg and can swallow capsules would provide an additional drug to prevent CINV. This reviewer therefore agrees with including this population in the label for aprepitant capsules.

c. Under and overdosing of aprepitant oral suspension in patients aged 6 months to 12 years

An Information Request (IR) was sent to the Applicant to provide information on underdosing and overdosing of aprepitant oral suspension in patients aged 6 months to <12 years in Protocols 208 and 134. This IR was requested because of dosing administration errors observed in the Human Factor studies. It was expected that additional information from the clinical trials would further characterize these dosing errors.

The Applicant provided the following data on under and over dosing of aprepitant oral suspension in pediatric patients aged 6 months to < 12 years in Protocols 208 and 134.

Underdosed

In Protocol 208, the Applicant defined underdose as an administered dose < 90% of protocol specified dose. Underdosing occurred in two patients:

- AN070529, who was randomized to the control regimen, received 40 mg of placebo for aprepitant, which was less than the protocol specified dose of 65.2 on Day 3. Reported AEs included: nausea (moderate severity), abdominal pain (moderate severity) and headache (mild severity). The Applicant considered all AEs as unrelated to the study drug.
- AN070808, who was randomized to the aprepitant regimen, received 15.5 mg, which was less than the protocol specified dose of 31.2 mg on Day 3. Reported AEs included: back pain, cough, anemia, decreased appetite, febrile neutropenia, decreased platelet count and upper respiratory infection. All were considered by the Applicant as mild in severity and unrelated to the study drug.

In Protocol 134, subjects were administered either a single dose (Part II or a three day regimen (Part IV) of aprepitant oral suspension. Using a similar definition as in Protocol 208, the Applicant identified one subject who was underdosed in Protocol134 (Part II):

- AN10189 who was administered 74mg of aprepitant instead of 103.6 mg. Adverse events reported in this patient included vomiting (mild severity),

abdominal pain (mild severity), headache (mild severity) and neutropenia (moderate severity).

There were no identified cases of underdosing in the 20 subjects in Part IV.

Overdosed

In Protocols 208 and 134, all overdoses were required to be reported to the Sponsor. An overdose was defined in Protocol 208 as a single dose greater than the allocated dose of study medication. In Protocol 134, an overdose was defined as a single dose exceeding the permitted maximum daily dose for each dose level of either oral or IV study drug. If an AE resulted from the overdose, the AE was to be reported as a serious adverse event, even if no other criteria for serious are met. If the overdose was not associated with any clinical symptoms or abnormal laboratory results, the overdose was reported as a non-serious Event of Clinical Interest (ECI) using the terminology “accidental or intentional overdose without adverse event”.

Protocol 208

There were five subjects who experienced an accidental overdose in Cycle 1. Of these, one subject received an overdose of aprepitant and four subjects received an overdose of placebo for aprepitant. In the case of the subject who received an overdose of aprepitant (AN070412), the site used an incorrect subject weight to calculate the weight-based dose adjustment. Of the four subjects who received an overdose of placebo for aprepitant; two were due to incorrect subject weight or incorrectly calculated weight-based dose adjustment (AN070408 and AN070403) and two were due to nursing errors, in which one subject received the Day 1 dose of 3.0 mg/kg on Day 2 instead of 2.0 mg/kg (AN071301), and one subject received 0.19 mL more than prescribed (AN070936). Three of the five accidental overdoses in Cycle 1 occurred at the same site (Site 0045).

There were six subjects 6 months to <12 years of age who experienced an accidental overdose in Cycles 2-6, two of which also experienced an accidental overdose in Cycle 1 (AN070408 and AN070403). Of the accidental overdoses in Cycles 2-6, four were due to nursing errors, two were due to incorrect weight used to calculate the weight-based dose adjustment, and one was due to a parent error. Of the four nursing errors: one nurse followed the Day 1 instructions, rather than the Day 2 instructions resulting in administration of a Day 1 dose on Day 2 of Cycle 3 (AN070601) and one sub-investigator made an error in transcribing the dose adjustment, prescribing 3 mg/kg on Days 2 and 3 of Cycle 5, rather than 2 mg/kg (AN071314). One subject (AN070418) experienced two accidental overdoses: on Day 2 of Cycle 2, the nurse could not recall exactly how much of the aprepitant suspension was administered to the subject, but copied the same dose transcribed for Day 1 (site was not able to confirm the actual dose administered), and on Day 1 of Cycle 3, the nurse administered the full 5 mL dose of study medication rather than the 125 mg equivalent based on a weight of 60 mg (2.4 mL). In the case of the

parent error (AN070407), following administration of the Day 1 dose of Cycle 2, a parent was given the Day 2 and 3 doses to take home and administer on Days 2 and 3, but due to a misunderstanding the parent gave the Day 2 dose on Day 1.

Table 3: Protocol 208 Overdose Details

Allocation Number	Cycle/Day	Per Protocol Dose	Actual dose
070408	Cycle 1/Day 1	69 mg	72 mg
	Cycle 1/Day 2	46 mg	48 mg
	Cycle 1/Day 3	46 mg	48 mg
	Cycle 2/Day 1	70.8 mg	72 mg
	Cycle 2/Day 2	47.2 mg	48 mg
070403	Cycle 1/Day 1	93.6 mg	96 mg
	Cycle 2/Day 1	93.9 mg	96 mg
	Cycle 2/Day 2	62.4 mg	64 mg
	Cycle 2/Day 3	62.4 mg	64 mg
071301	Cycle 1/Day 2	20.8 mg	31.2 mg
070412	Cycle 1/Day 1	87.9 mg	92.5 mg
	Cycle 1/Day 2	58.6 mg	62.5 mg
	Cycle 1/Day 3	58.6 mg	62.5 mg
070936	Cycle 1/Day 1	1.05 ml/ 26.2 mg	1.2 ml/ 30 mg
070407	Cycle 2/Day 1	75 mg	125 mg
070418	Cycle 2 /Day 2	38.6 mg	57.9 mg
	Cycle 3/Day 1	60 mg	125 mg

070601	Cycle 3/Day 2	77.1 mg	115.6 mg
071314	Cycle 5/Day 2	15 mg	22 mg
	Cycle 5/Day 3	15 mg	22 mg

Applicant's table

Protocol 134

There were two subjects who experienced an overdose in Part II. At the time Part II was conducted, subjects were dosed based on body surface area (BSA). One subject (AN 10122) experienced an overdose as the BSA was calculated incorrectly leading to an error in the volume of aprepitant suspension administered. The other subject, AN10135 also had an error with the BSA that led to an overdose. There were no identified cases of overdose in the 20 randomized subjects 6 months to <12 years of age in Part IV of Protocol 134.

Table 4: Protocol 134 Overdose Details

Allocation Number	Day	Per Protocol Dose	Actual dose
10122	Day 1	91.76 mg	113.96 mg
10135	Day 1	18 mg	20 mg

Adverse Events Overdosing

Table 5: Listing of AEs Protocol 208 for Underdosing

Study ID	Subject ID	Preferred Term	Serious Event	AE Relative to Treatment Start in Cycle 1	AE Duration	Duration	Intensity	Action Taken with Study Medication	Relationship	AE Outcome	EPOCH
0869-208_003200014	070529	Nausea	N	1	5	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Abdominal pain upper	N	2	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Headache	N	3	12	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
0869-208_003500001	070808	Back pain	N	3	2	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Cough	N	3	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Anaemia	N	11	5	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Decreased appetite	N	11	1	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Febrile neutropenia	Y	12	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Platelet count decreased	N	12	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Upper respiratory	N	12	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment cycle 1

Table 6: Listing of AEs Protocol 208 for Overdosing

Study ID	Subject ID	Preferred Term	Serious Event	AE Relative to Treatment	AE Duration	Duration	Intensity	Action Taken with Study Medication	Relationship	AE Outcome	EPOCH
0869-208_00450004	070403	Accidental overdose	N	1	1	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Accidental overdose	N	22	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Febrile neutropenia	Y	34	3	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Accidental overdose	N	43	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
0869-208_00250001	070407	Accidental overdose	N	41	23.9997	HOURS		DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Somnolence	N	41	2.1429	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Decreased appetite	N	42	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Pyrexia	Y	42	14.25	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Anaemia	N	63	40	MINUTE	MILD	DOSE NOT	NOT	RECOVERED	Cycle 2

		Vomiting	N	69	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Decreased appetite	N	76	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
0869-208_004500005	070408	Accidental overdose	N	1	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Febrile neutropenia	Y	12	5	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Allergic transfusion reaction	N	13	23	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Electrolyte imbalance	N	13	23	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Purulence	N	25	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Accidental overdose	N	37	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Renal tubular disorder	Y	44	1.2857	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Thrombocytopenia	N	44	1.1429	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Stomatitis	N	45	1.4286	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2

0869-208_00450007	*070412 (received aprepitant)	Accidental overdose	N	1	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Febrile neutropenia	Y	8	4	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
0869-208_00350004	070418	Accidental overdose	N	49				DOSE NOT CHANGED	NOT RELATED		Cycle 2
		Vomiting	N	56	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Nausea	N	58	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Anaemia	N	60	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Febrile neutropenia	Y	60	1.4286	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Vomiting	N	60	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Abdominal pain	N	61	5	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Stomatitis	N	62	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Accidental overdose	N	78				DOSE NOT CHANGED	NOT RELATED		Cycle 2

		Anaemia	N	78	1.5714	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
0869-208_00450006	070601	Accidental overdose	N	80	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 3
0869-208_00270005	070936	Accidental overdose	N	1	3	DAYS		DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Pneumonia	Y	10	1.1429	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Pancytopenia	Y	11	6	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
0869-208_00360001	071301	Accidental overdose	N	2	5	MINUTES	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Febrile neutropenia	Y	5	2.7143	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
0869-208_00230005	071314	Accidental overdose	N	93	2	DAYS		DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Nausea	N	93	1.5714	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypotension	N	95	1	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5

		Vomiting	N	95	3	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Blood creatinine increased	Y	97	5	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Acidosis	N	98	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	99	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypophosphataemia	N	100	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Neutropenia	N	100	2.2857	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	101	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Febrile neutropenia	Y	103	1.8571	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypophosphataemia	N	103	4	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypotension	N	103	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Melaena	N	103			MILD	DOSE NOT CHANGED	NOT RELATED	UNKNOWN	Cycle 5
		Thrombocytopenia	N	103	7.4669	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5

		Abdominal pain	N	104	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	105	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	106	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Thrombocytopenia	N	108	3	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Abdominal pain	N	113	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Anaemia	N	113	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Fall	N	113	1.0169	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Subcutaneous haematoma	N	113	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Thrombocytopenia	N	113	23.4669	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Diarrhoea	N	114	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	115	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5

Applicant's table
In cycles 2-6 all subjects received aprepitant oral suspension
*Only one subject in cycle 1 - 070412 received aprepitant oral suspension

Reviewer's comments: Per the Applicant's response, of the nine subjects who experienced an accidental overdose in Protocol 208 (cycle 1 and cycles 2 to 6), four were from the same site (site 0045). Two of the four subjects each experienced two accidental overdoses at site 0045, for a total of six accidental overdoses at that site. Of the six accidental overdoses at that particular site, five were due to an incorrect weight being used to calculate the adjusted dose of aprepitant to be administered.

Unlike in the HF studies which were not set up to actually calculate patient weight, weight calculation errors were the primary issue in the clinical trial, specifically at one particular site. Other nursing and parent errors related to dosing errors in the clinical trials, confirmed the errors that were observed in the HF studies.

Concerning the AEs observed in the underdosing of the subject who received aprepitant, the AE of nausea could possibly be related to decreased efficacy of the lower aprepitant dose. Of the nine subjects in P208 who received overdosing none of the reported AEs the Applicant stated that none were related to the study drug. The reported AEs, such as febrile neutropenia, thrombocytopenia and anemia, would not be unusual In this patient population with a malignancy diagnosis and receiving chemotherapeutic agents.

(b) (4)

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/s/

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08/28/2015

DONNA J GRIEBEL
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