Clinical Pharmacology Review Addendum

NDA	21549/S-025; (b) (4)
Submission Date	03/04/2014
Drug	Emend (aprepitant)
Submission Type; Code	Pediatric Supplement
Indication	Prevention of CINV (b) (4) (NDA 21549/S-025 Emend Capsules (b) (4) (b) (4) (b) (4)
Applicant	Merck Sharp & Dohme
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Summary

(b) (4) (b) (4) the Clinical Pharmacology review team was asked to evaluate whether pharmacokinetic (PK) data supported modifying the proposed pediatric dosing for the aprepitant capsule to include pediatric patients less than 12 years who weighed at least 30 kg since their weight based dose for the suspension formulation is equivalent to the adolescent (and adult) dose.

In the phase 3 efficacy trial, pediatric patients less than 12 years who weighed at least 30 kg received oral suspension. (b) (4) (b) (4) The review team raised the question whether the capsule formulation could be used in patients less than 12 years who weighed at least 30 kg and can swallow oral capsules.

There was no dedicated relative bioavailability study (b) (4) . Furthermore, the PK sampling schedule in the efficacy trial also limited the ability to assess the relative bioavailability (b) (4) . Therefore, population PK analysis was conducted to address this question. Please refer to the clinical pharmacology review by Dr. Elizabeth Shang for other details of the NDA review.

The population pharmacokinetics analysis indicated that body weight, age and dose are significant covariates for apparent clearance, and body weight is a significant covariate for apparent volume of distribution. The type of formulation was not found to be a significant covariate on bioavailability. The clearance for patients aged 12 through 17 years was similar to 16 patients aged less than 12 years who weighed at least 30 kg. The median clearance was 4.4 L/h in 48 patients aged 12 through 17 years, and 4.8 L/h in 16 patients aged less than 12 years who weighed at least 30 kg. As a result, no significant difference of aprepitant AUC is anticipated between the two formulations. In addition, when pediatrics less than 12 years who weighed at least 30 kg were included with pediatrics age 12-17 years for the efficacy analysis (see Table 1 provided by Clinical Review), the EMEND arm had better efficacy compared to placebo for the primary and secondary endpoints.

Overall, it was recommended that the available PK data supported extending the dosing using capsule formulation in children less than 12 years who weighed at least 30 kg.

Table 1: Efficacy Endpoint Responses for Patients Aged 12 to 17 Years and Patients less than 12 Years Who Weighed at least 30 kg

	EMEND Regimen n/m (%)	Control Regimen n/m (%)
Patients Aged 12 to 17 Years or Body Weight ≥ 30 kg		
PRIMARY ENDPOINT		
Complete Response* - Delayed phase	31/63 (49.2)	13/69 (18.8)
OTHER PRESPECIFIED ENDPOINTS		
Complete Response* – Acute phase	35/63 (55.6)	26/69 (37.7)
Complete Response* – Overall phase	22/63 (34.9)	9/69 (13.0)

*Complete Response = No vomiting or retching and no use of rescue medication.
n/m = Number of patients with desired response/number of patients included in time point.
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

Note: Included in this table are 47 subjects 12 to 17 years of age (weight range 28 to 104 kg) and 16 subjects 6 to <12 years of age (weight range 30 to 63 kg) in the EMEND regimen group. The control regimen group includes 48 subjects 12 to 17 years of age (weight range 33 to 135 kg) and 21 subjects 6 to <12 years of age (weight range 30 to 66 kg). The subset of 37 subjects aged 6 to <12 years and weighing ≥30 kg represents 44% of the total number (84) of subjects aged 6 to <12 years included in the efficacy analysis. All subjects aged 12 to 17 years are included here.

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