Clinical Pharmacology Review

PRODUCT (Generic Name):	Memantine
PRODUCT (Brand Name):	Namenda
DOSAGE FORM:	Capsules
INDICATION:	Autism Spectrum Disorder
DOSAGE STRENGTHS:	(b) (4)
NDA:	022525
SUBMISSION DATE:	January 6, 2014
SPONSOR:	Forest Research
REVIEWER	Andre Jackson

REVIEW OF PEDIATRIC STUDY

1. EXECUTIVE SUMMARY

The NDA for memantine extended release (ER) capsule was filed in response to a written request issued on January 25, 2012 and amended on May 29, 2013 in children 6-12 years old with Autism Spectrum Disorder (ASD). (b) (4)

(b) (4)

The sponsor has conducted a single dose pharmacokinetic study with the 3 mg ER capsule in pediatric patients 5 to 16 years of age and submitted the study report prior to the issuance of the written request. The Office of Clinical Pharmacology has concluded that the study is sufficiently designed and conducted to characterize memantine pharmacokinetics in pediatric patients at the target age range (6-12 years). The pharmacokinetic study results were applied to support the pediatric doses in the efficacy and safety studies. Hence no additional pediatric pharmacokinetic study has been required as part of the written request.

The pediatric pharmacokinetic study report is included in the current submission. Study results indicated that across the studied age range (5-16 years), the Tmax occurred at 24-30 hrs and the half-life was approximately 45 hrs. AUC and Cmax increased as a patient's body weight decreased.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA.

1.2 Labeling Recommendations:

We recommend that no pediatric pharmacokinetic information be included under Section 8 of the label. Memantine has been approved for the treatment of moderate to severe dementia of the Alzheimer's type. The approved indication does not target a disease in pediatric patients. In addition, the results from the efficacy and safety studies for ASD are negative. Hence, from the OCP's perspective, the usage of memantine in pediatric patients should not be implied or suggested in the label.

2. QUESTIONS BASED REVIEW

2.1 Was the pharmacokinetics of memantine influenced by the subject's weight?

Yes. The AUC inf and Cmax were higher for the lower weight children (Table 1).

Table 1. Pharmacokinetic Parameters (Mean ± SD)

PK Parameter	*Group A (60 - 80 kg) (n = 2)*	*Group B (40 - 59 kg) (n = 5)*	*Group C (20 - 39 kg) (n = 5)*	*Group D (< 20 kg) (n = 2)*
C_{max}, ng/mL	2.58 ± 0.21	4.30 ± 0.80	6.92 ± 1.63	8.03 ± 2.44
T_{max}, h	24.00 ± 0.00 24.00 (24.00, 24.00)[a]	26.44 ±3.29 24.13 (24.00, 30.08)[a]	23.61 ± 11.25 29.98 (4.02, 30.00)[a]	27.04 ± 4.22 27.04 (24.05, 30.02)[a]
AUC_{0-t}, ng•h/mL	196.2 ± 39.5	362.3 ± 80.8	546.9 ± 77.6	636.2 ± 165.3
$AUC_{0-\infty}$, ng•h/mL	226.5 ± 31.0	406.0 ± 105.0	596.2 ± 102.6	709.8 ± 191.3
$T_{½}$, h	42.83 ± 9.61	48.74 ± 7.39	43.55 ± 11.62	48.51 ± 1.85

a Median (range)

2.2 Was the threshold AUCinf exposure of 2100 ng.h/ml for brain lesions established from the toxicology studies exceeded in the lowest weight children in the pharmacokinetic study?

No. The highest measured AUC inf of ~ 900 ng.h/ml did not exceed the established exposure limit of 2100 ng.h/ml.

2.3 Are the requirements on pediatric pharmacokinetic study from the written request fulfilled by the sponsor?

The pediatric pharmacokinetic study was conducted and submitted prior to the pediatric written request being issued. The Office of Clinical Pharmacology has determined that the study is sufficiently designed and conducted to characterize memantine pharmacokinetics in pediatric patients at the target age range (6-12 years). The pharmacokinetic study results were applied to support the pediatric doses in the efficacy and safety studies. Therefore, additional pediatric pharmacokinetics study has not been required as part of the written request.

3.0 Detailed Study Information

3.1 Pharmacokinetics- Single Dose Pediatric Pharmacokinetic Study

CLINICAL PHARMACOLOGY STUDY REVIEW

Single Dose Study	
Report #: MEM-PK-21	
Drug: Memantine	**NDA:**22525
Link	\\cdsesub1\evsprod\nda022525\0053\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\mem-pk-21\mem-pk-21.pdf
Title	A Single Dose, Open-Label Study Evaluating the Pharmacokinetics of an Oral Memantine HCl Modified-Release Formulation in Pediatric Patients With Autistic Spectrum Disorders
Objectives:	The objective of this study was to evaluate the pharmacokinetics of a single, low, oral dose of memantine HCl MR/ER formulation in four groups of pediatric patients with ASD stratified by body weight.
Rationale:	A single, oral dose of 3-mg memantine HCl ER was chosen for this study in order to ensure that exposure to memantine would be below the AUC0-∞ of 2100 ng•h/mL, which represented the 10% of the no observable effect level (NOEL) for brain lesions seen in a juvenile rat toxicology study.

Study Design:
This was an open-label, single-dose study conducted in four groups of pediatric patients with ASD, ages 5 to 16 years (inclusive), stratified by weight. Patients were assigned to one of 4 groups according to body weight, as an earlier population PK analysis demonstrated that differences in memantine plasma exposure could be attributed to a large extent to differences in weight

Enrollment proceeded sequentially by group, with Group A patients enrolling first and Group D patients enrolling last. Following enrollment of Group A, each subsequent group of patients was enrolled after 1) the pharmacokinetics of memantine were evaluated for at least two patients in the preceding group and 2) drug exposure in terms of AUC for patients in the preceding group was determined to be less than a predefined limit that was deemed to be safe. Enrollment in previous groups was closed if no additional PK data were needed for those weight groups.

Dose: 3 mg ER capsule

No. of Groups	4	**No. of subjects**	14	**No. of subjects/ group on Placebo**	NA
Doses	Group A: 60 to 80 kg- 3mg Group B: 40 to 59 kg- 3mg Group C: 20 to 39 kg- 3mg Group D: less than 20 kg-3 mg				
Administration	☐ Fast ☑ Fed For patients with difficulty swallowing, the capsule's contents were to be sprinkled onto a small amount (1 teaspoon) of refrigerated soft, wet foods that did not require chewing (eg, applesauce, yogurt, ice cream). The sprinkle/food mixture was to be swallowed immediately (chewing was to be avoided).				

Sampling Times	PK: 0.0 hour (predose) and 4, 8, 24, 30, 48, 96, and 168 hours

	postdose. PD:NA
PK Parameters	The following PK parameters in plasma were included: area under the plasma concentration versus time curve (AUC) from time zero to time t (AUC0-t) and from time zero to infinity (AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), and T½. The maximum plasma concentration of memantine was determined observationally as the peak concentration for each subject. Tmax was determined as the time corresponding to Cmax.
PK Analysis	Descriptive statistics (mean, standard deviation, minimum, maximum, median, and coefficient of variation) are provided per weight group for all PK parameters (Cmax, AUC0-t, AUC0-∞, Tmax, and T½) based on the PK Population.
PD Endpoint(s)	NA
PD Parameters	NA
Safety Measures	Analysis of the clinical safety data was performed following a formal statistical analysis plan.

Analytical Method

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	Memantine Hydrochloride		

Initiation Date: August 2007
Completion Date: December 2009

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Notes:

Results

Study Population

Randomized Treated Completed Discontinued Due to AE PK Population/Safety Population	14 14 14 0 14
Age [Mean (range)]	9.8(5-16)
Male/Female	12/2
Race (Caucasian/Black/Asian/Hispanic)	12/2

Results:

Table 1. Pharmacokinetic Parameters (Mean ± SD)

PK Parameter	*Group A (60 - 80 kg) (n = 2)*	*Group B (40 - 59 kg) (n = 5)*	*Group C (20 - 39 kg) (n = 5)*	*Group D (< 20 kg) (n = 2)*
C_{max}, ng/mL	2.58 ± 0.21	4.30 ± 0.80	6.92 ± 1.63	8.03 ± 2.44
T_{max}, h	24.00 ± 0.00 24.00 (24.00, 24.00)[a]	26.44 ±3.29 24.13 (24.00, 30.08)[a]	23.61 ± 11.25 29.98 (4.02, 30.00)[a]	27.04 ± 4.22 27.04 (24.05, 30.02)[a]
AUC_{0-t}, ng•h/mL	196.2 ± 39.5	362.3 ± 80.8	546.9 ± 77.6	636.2 ± 165.3
$AUC_{0-\infty}$, ng•h/mL	226.5 ± 31.0	406.0 ± 105.0	596.2 ± 102.6	709.8 ± 191.3
$T_{½}$, h	42.83 ± 9.61	48.74 ± 7.39	43.55 ± 11.62	48.51 ± 1.85

a Median (range)

Table 2. Incidence of Treatment-Emergent Adverse Events by Weight Group

System Organ Class *Preferred Term*	*Group A (N = 2) n (%)*	*Group B (N = 5) n (%)*	*Group C (N = 5) n (%)*	*Group D (N = 2) n (%)*	*All Patients (N = 14) n (%)*
At least 1 TEAE	**0**	**2 (40.0)**	**0**	**1 (50.0)**	**3 (21.4)**
Cardiac disorders	**0**	**1 (20.0)**	**0**	**0**	**1 (7.1)**
Sinus bradycardia	0	1 (20.0)	0	0	1 (7.1)
General disorders and administration site conditions	**0**	**0**	**0**	**1 (50.0)**	**1 (7.1)**
Vessel puncture site haematoma	0	0	0	1 (50.0)	1 (7.1)
Injury, poisoning and procedural complications	**0**	**1 (20.0)**	**0**	**0**	**1 (7.1)**
Excoriation	0	1 (20.0)	0	0	1 (7.1)
Sunburn	0	1 (20.0)	0	0	1 (7.1)
Investigations	**0**	**1 (20.0)**	**0**	**0**	**1 (7.1)**
Blood pressure diastolic decreased	0	1 (20.0)	0	0	1 (7.1)

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

What is the selected maximum pediatric dose?
The maximum pediatric dose was selected to maintain memantine level below the AUC0-∞ of 2100 ng•h/mL, which approximately equivalents to the administration of 12 mg to children with body weight of 60 -80 kg.
What is the basis for considering this dose to be the maximum pediatric dose?
The maximum pediatric dose represented 10% of the no observable effect level (NOEL) for brain lesions obtained in a juvenile rat toxicology study.

Comments:

1. Tmax and Cmax were similar among all body weight groups. The Tmax occurred at 24-30 hrs and the half-life was ~ 45 hrs.
2. Cmax and AUC increased as a patient's body weight decreased following the administration of the fixed dose of 3 mg.
3. Drug exposure in terms of AUC for patients in the pharmacokinetic study was determined to be less than a predefined limit (2100 ng•h/mL) that was deemed to be safe.
4. The study design and results are acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDRE J JACKSON
05/21/2014

HAO ZHU
05/21/2014