CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206439Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	206439
DATE RECEIVED BY ONDQA:	October 17, 2014
DRUG NAME:	Namzaric
GENERIC NAME	Memantine HCl ER/Donepezil Capsules
DOSAGE FORM:	Tablet
STRENGTH	14 mg 10 mg, 28 mg / 10 mg
INDICATION:	Treatment of moderate to severe dementia of the Alzheimer's type.
SPONSOR:	Forest Laboratories, Inc.
REVIEW FINISHED:	October 27, 2014
NAME OF STATISTICAL REVIEWER:	Xiaoyu (Cassie) Dong, Ph.D.

_____

Reviewer: Xiaoyu Dong, Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____

Meiyu Shen, TL, Mathematical Statistician, CDER/OTS/OB/DB VI

Distribution: NDA 206439
CDER/OTS/OB/DB VI/ Yi Tsong
CDER/OTS/OB/DB VI/ Meiyu Shen
CDER/OTS/OB/ Lillian Patrician
CDER/ONDQA/Pei-I Chu
CDER/ONDQA/ Okpo Eradiri
CDER/ONDQA/ Teshara G, BOUIE

TABLE OF CONTENTS

List of Figures

I. EXECUTIVE SUMMARY

We performed statistical analysis of 12 months long-term dissolution stability data at 1h, 4h, 8h, and 12h for Memantine HCl ER (b) (4) manufactured by Forest Research for the strength of 14 mg / 10 mg and 28 mg/10 mg.

The results are summarized in Table 1.As it shows, the shelf life for each strength is not able to be established because most of the observations at 4h and 8h are out of the specification proposed by FDA. More specifically, the dissolution results at 4h and 8h are in general too high compared to the upper limit of the acceptance criteria. Revision and finalization of the specifications may be needed for this combined drug product.

Please see section III for detailed stability analysis results.

Table 1 - FDA Statistics Reviewer's Estimated Shelf Life for each Strength using Long-term Dissolution Stability Data and FDA's Proposed Specification

Strength	1h	4h	8h	12h
14 mg / 10 mg	18 months	Most observations are out of the upper limit of the proposed acceptance criteria		18 months
28 mg/10 mg	18 months			18 months

II. INTRODUCTION

The sponsor submitted the long-term stability data of dissolution testing up to 12 months for the following batches as listed in Table 2. The product of each batch was packaged in bottle configurations of 30 counts and 90 counts as shown in Table 3.

Table 2: Available Long-Term Stability Data

Table 4-1. Summary of Bach Information and Stability Protocols

Strength	*SAP Code*	*FRI Lot#*	*Study ID*
14/10mg	19118	BN00023907	MDX-13-004-001 (microbiology) & MDX-13-005-001
		BN00023908	
		BN00023909	
28/10mg	19106	BN00023559	MDX-13-001-001 & MDX-13-001-002 (microbiology)
		BN00023560	
		BN00023561	

Table 3: Package Configurations

Table 3-1. NDA Registration Batches - Container Closure System

Capsule Count	*Strength (mg)*	*Bottles*	*Caps*
30	28 mg/10 mg & 14 mg/10 mg	S/60CC/HDPE/BOTTLE/WHITE/ (b) (4) (b) (4)	33MM/CR/WHITE/CAP/ (b) (4) (b) (4)
90		S/120CC/HDPE/BOTTLE/WHITE/ (b) (4) (b) (4)	38MM/CR/WHITE/CAP/ (b) (4) (b) (4)

The dissolution testing results for Memantine ER (b) (4) were obtained at 1h, 4h, 8h, and 12h for each batch and each configuration at the long-term storage condition. The FDA's proposed specifications are listed below in Table 4.

Table 4 – FDA Proposed Acceptance Criteria for Dissolution Testing at Each Time Point

Strength	1h	4h	8h	12h
Acceptance Criteria	(b) (4) %	(b) (4) %	(b) (4) %	NLT (b) (4) %

III. FDA STAT REVIEWER'S ANALYSES

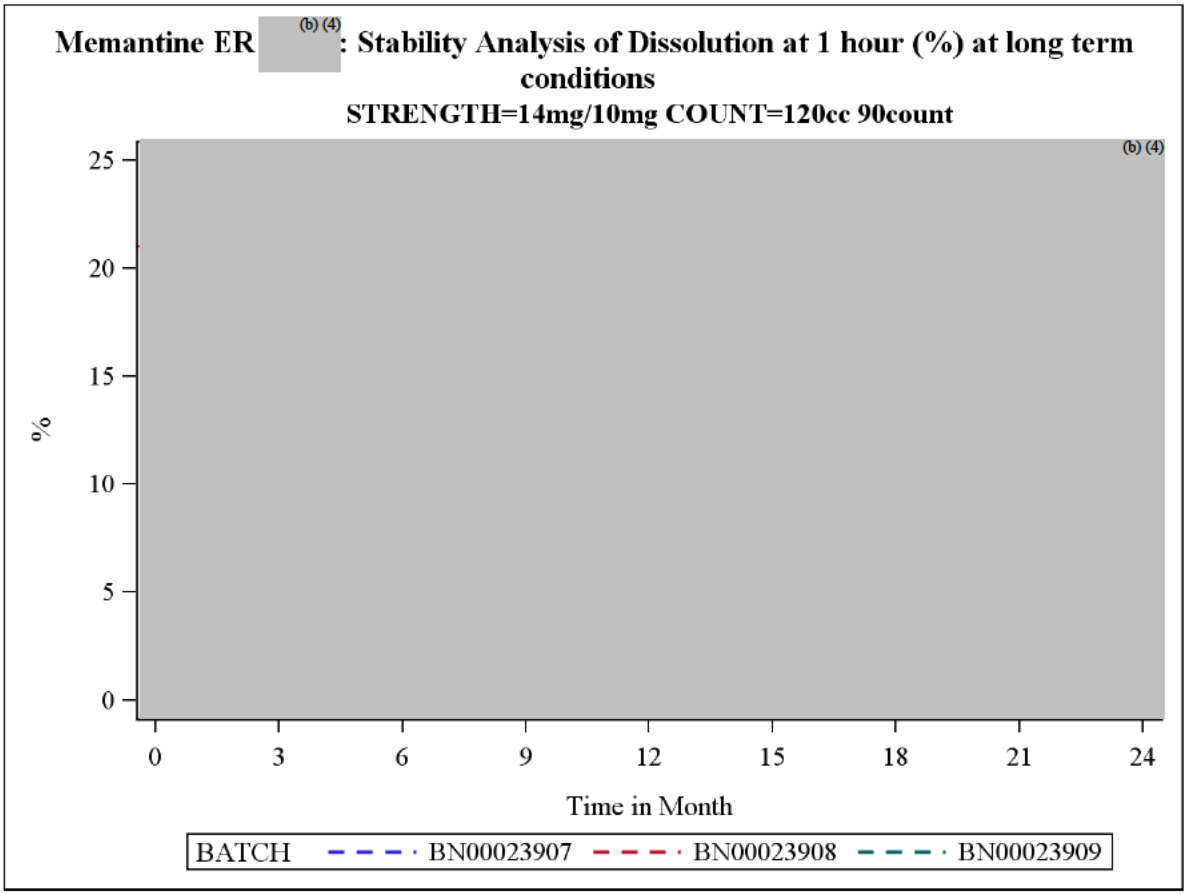
We performed statistical analysis of 12 months long-term dissolution stability data at 1h, 4h, 8h, and 12h for Memantine HCl ER (b) (4) manufactured by Forest Research for the strength of 14 mg / 10 mg and 28 mg/10 mg. The results are summarized as below.

- For 1hr average dissolution data, the estimated shelf life using 12-months long term data is 18 months with an acceptance criterion of NMT (b) (4) %;
- For 4hr average dissolution data, the estimated shelf life using 12-months long term data cannot be obtained with acceptance criteria of (b) (4) % because most of the data points are out of upper limit of the specification. In addition, the data of three batches at each strength cannot be pooled due to significant batch effect.
- For 8hr average dissolution data, the estimated shelf life using 12-months long term data cannot be obtained with acceptance criteria of (b) (4) %. %, because most of the data points are out of upper limit of the specification. In addition, the data of three batches at each strength cannot be pooled due to significant batch effect.

- For 12 hr average dissolution data, the estimated shelf life using 12-months long term data is 18 months with an acceptance criterion of NLT (b) (4) %;

The stability plots of 1h, 4h, 8h, and 12h dissolution data from three batches listed in Table 2 are provided below. In those plots, red straight lines are the FDA proposed acceptance criteria; the dashed curves are the 95% confident limits. The estimated shelf life would be the shortest intersect of the dashed line (95% confidence limits) with the limits of the acceptance criteria.

Figure 1 : Stability Plots of Average 1-Hour Dissolution at 14 mg/ 10 mg Strength from FDA Statistical Reviewer's Analysis (the dash lines are the 95% one-sided confidence interval of the mean response, the solid line is the mean response from regression analysis; the red straight line is the FDA's proposed specification of (b) (4) %)



16 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

XIAOYU DONG
10/27/2014

MEIYU SHEN
10/27/2014