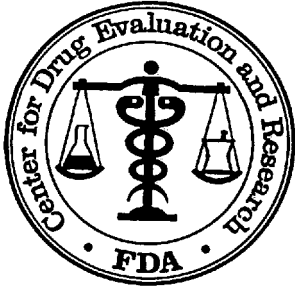


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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

I. EXECUTIVE SUMMARY 4

II. INTRODUCTION..... 4

III. FDA STAT REVIEWER'S ANALYSES 5

List of Figures

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)%). 6

Figure 2 : Stability Plots of Average 1-Hour Dissolution at 28 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)%). 8

Figure 3 : Stability Plots of Average 4-Hour Dissolution at 14 mg/ 10 mg Strength from FDA Statistical Reviewer’s Analysis (the dash curves are the 95% two-sided confidence interval of the mean response, the solid line is the mean response from regression analysis; the red straight lines are the FDA’s proposed specification of (b)(4)%). 9

Figure 4 : Stability Plots of Average 4-Hour Dissolution at 28 mg/ 10 mg Strength from FDA Statistical Reviewer’s Analysis (the dash curves are the 95% two-sided confidence interval of the mean response, the solid line is the mean response from regression analysis; the red straight lines are the FDA’s proposed specification of (b)(4)%). 12

Figure 5 : Stability Plots of Average 8-Hour Dissolution at 14 mg/ 10 mg Strength from FDA Statistical Reviewer’s Analysis (the dash curves are the 95% two-sided confidence interval of the mean response, the solid line is the mean response from regression analysis; the red straight lines are the FDA’s proposed specification of (b)(4)%). 15

Figure 6 : Stability Plots of Average 8-Hour Dissolution at 28 mg/ 10 mg Strength from FDA Statistical Reviewer’s Analysis (the dash curves are the 95% two-sided confidence interval of the mean response, the solid line is the mean response from regression analysis; the red straight lines are the FDA’s proposed specification of (b)(4)%). 18

Figure 7 : Stability Plots of Average 12-Hour Dissolution at 14 mg/ 10 mg Strength from FDA Statistical Reviewer’s Analysis (the dash curves 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 NLT (b)(4)%). 21

Figure 8 : Stability Plots of Average 12-Hour Dissolution at 28 mg/ 10 mg Strength from FDA Statistical Reviewer’s Analysis (the dash curves 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 NLT (b)(4)%). 22

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 Batch Information and Stability Protocols

<i>Strength</i>	<i>SAP Code</i>	<i>FRI Lot#</i>	<i>Study ID</i>
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	

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.