CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205703Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NDA Number	205703
Drug Name	Esmolol HC1 Premixed Injection
Indication(s)	Supraventricular tachycardia (b) (4) (Esmolol Hydrochloride) is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstance where short term control of ventricular rate with a short-acting agent is desirable. Brevibloc is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the heart rate requires specific intervention.
Dosage Form	Solution, Injection
Applicant	HQ Specialty Pharma Corp
Date(s)	Date Received Consult Request: 1/22/2014 Completion Date: 1/30/2014
Review Priority	Standard
Biometrics Division	VI
Statistical Reviewer	Youngsook Jeon, Ph.D.
Concurring Reviewer	Meiyu Shen, Ph.D.
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1. EXECUTIVE SUMMARY

The purpose of this review is to provide statistical assessment on the HQ Specialty Pharma's long-term stability data of Esmolol Premixed Injection 2500mg/250mL and 2000mg/100mL drug products so that FDA Office of New Drug Quality Assessment can make an informed decision on the approval of the proposed (b) (4) month shelf life.

Based on the submitted 12-month stability data, our stability analysis shows that the estimated shelf life for pH of the 2000mg/100mL drug product is 20 months; therefore, the current stability data does not support the proposed 24-month shelf life for the 2000mg/100mL drug product. To support the proposed shelf life, the sponsor may provide 18- or 24-month stability data for pH of the 2000mg/100mL product and the updated stability analysis results.

2. INTRODUCTION

The purpose of this review is to provide statistical assessment on the HQ Specialty Pharma's long-term stability data of Esmolol Premixed Injection 2500mg/250mL and 2000mg/100mL drug products so that FDA Office of New Drug Quality Assessment can make an informed decision on the approval of the proposed (b)(4)-month shelf life.

HQ Specialty Pharma manufactured three registration batches of Esmolol Hydrochloride Premixed Injection 2500mg/250mL (10mg/mL) and three registration batches of Esmolol Hydrochloride Double Strength Premixed Injection 2000mg/ 100mL (20mg/mL) in August 2012 and placed them into the stability program. The stability batches are stored at accelerated temperature (40°C ± 2°C, 15% ± 5% RH) and long-term room temperature (25°C ± 2°C, 40% ± 5% RH).

The sponsor evaluated the long-term stability data of 12 months and concluded that the Esmolol Premixed products are expected to comply within a (b)(4)-month expiration period at controlled room temperature of 15°C to 30°C.

This review summarizes the sponsor's data and study report in Section 3 and describes the FDA statistical reviewers' assessments on the sponsor's submission in Section 4.

3. SPONSOR'S SUBMISSION

This section provides the summary of the sponsor's data and study report.

3.1 Data

Table 1 presents the summary of the long-term stability data of Esmolol Premixed Injection product in two presentations: 2000mg/100mL (20mg/mL strength) and 2500mg/250mL (10mg/mL strength).

Table 1. Summary of Long-term Stability Data

Strength	Batch	Available Data
20mg/mL	2R005	12 months
	2R006	12 months
	2R007	12 months
10mg/mL	2R008	12 months
	2R009	12 months
	2R010	12 months

3.2 Study Report

Sponsor's stability study report, 3.2.P.8.1 Stability Summary and Conclusions, contains some analysis results of stability data including linear regression graphs for potency (Assay) and Esmolol Free Acid, the major degradants (also known as (b) (4)); however, it lacks an appropriate stability analysis.

4. REVIEWER'S ASSESSMENT

This section describes the FDA statistical reviewers' statistical evaluation on the sponsor's submission and provides recommendations if applicable.

4.1 Statistical Evaluation

We conducted stability analyses in accordance with ICH Q1E Evaluation of Stability Data. Among 20 stability parameters, 5 of them have data that are amenable to statistical analyses. These parameters are: pH, Osmolality, Assay, Esmolol Free Acid, and Total Degradants. Table 2 shows the summary of estimated shelf lives for these stability parameters for each drug product strength.

Table 2. Estimated Shelf Life

Strength	Parameter	Specification	Estimated Shelf Life
20mg/mL	pH	4.5 - 6.5	(b) (4) months
	Osmolality	440 - 500	months
	Assay	(b) (4)	months
	Esmolol Free Acid	<= (b) (4)	months
	Total Degradants	<=	months
10mg/mL	pH	4.5 - 6.5	months
	Osmolality	320 - 450	months
	Assay	(b) (4)	months
	Esmolol Free Acid	<= (b) (4)	months
	Total Degradants	<=	months

All estimated shelf lives are longer than the proposed shelf life of (b) (4) months except for pH of 20mg/mL drug product. Its estimated shelf life is only 20 months, which is (b) (4) than the proposed shelf life (see Figure 1). The sponsor's long-term stability data does not support the proposed shelf life for 20mg/mL drug product.

Figure 1. Fitted Regression Lines and 90% Confidence Bounds for pH of 20mg/mL Drug Product

4.2 Conclusions and Recommendations

Our stability analysis shows that the estimated shelf life for pH of 20mg/mL drug product is 20 months; therefore, the current stability data does not support the proposed (b) (4)-month shelf life for 20mg/mL drug product. On the other hand, the proposed shelf life for 10mg/mL product is well supported by the submitted 12-month stability data.

To support the proposed shelf life for 20mg/mL drug product, the sponsor may provide 18- or 24-month stability data for pH of 20mg/mL product and the updated stability analysis results. However, given decreasing trend of pH of 20mg/mL product, updated stability data may not support the proposed shelf life.

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/s/

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01/31/2014

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01/31/2014