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APPLICATION NUMBER:

205703Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	04-04-2014
From	Kasturi Srinivasachar, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205703
Supplement#	
Applicant	HQ Specialty Pharma Corporation
Date of Submission	June 28, 2013
PDUFA Goal Date	April 28, 2014
Proprietary Name / Established (USAN) names	Esmolol Hydrochloride Premixed Injection
Dosage forms / Strength	Sterile solution, 2500 mg/250 mL and 2000 mg/100 mL
Proposed Indication(s)	1. Supraventricular Tachycardia (SVT) 2. Intraoperative and Postoperative Tachycardia and/or 3. Hypertension
Recommended:	Approval

This secondary review is based on the primary reviews of:

- CMC (Pei-I Chu), 02-26-2014
- Quality Biopharmaceutics (Mahayni Houda), 03-20-2014
- Microbiology (Denise Miller), 02-26-2014
- DMEPA (Loretta Holmes), 03-10-2014 and 12-30-2013
- Biometrics Consult (Youngsook Jeon), 01-31-2014
- Pharmacology/Toxicology (Philip Gatti), 09-03-2013

1. Introduction

This is a 505(b)(2) NDA for esmolol hydrochloride injection, 2500mg/250 mL (10 mg/mL) and 2000mg/100 mL (20 mg/mL). This filing is based upon the reference listed drug (RLD), Brevibloc Premixed Injection, which was approved on Dec. 31, 1986 under NDA 19386. Since there is a change in the formulation, this NDA does not qualify for the 505(j) submission pathway.

2. Background

Brevibloc is a cardio-selective beta-adrenergic receptor blocking agent administered intravenously and has a very short duration of action with an elimination half-life of approximately 9 minutes. It is indicated for:

- 1) Control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter and control of heart rate in noncompensatory tachycardia
- 2) Control of perioperative tachycardia and hypertension.

The current application relies on the Agency's determination of safety and efficacy for Brevibloc and supporting relevant published literature and consequently there are no clinical or clinical pharmacology sections. The regulatory decision will be primarily based on the recommendations in the CMC, Quality Microbiology, Biopharmaceutics, Nonclinical Pharmacology and Toxicology and Division of Medication Error Prevention and Analysis (DMEPA) reviews of this application.

3. CMC

The reviewer recommends approval from a CMC perspective.

Drug Substance: The Applicant referenced DMF (b) (4) for the drug substance information. The reviewer states that this DMF and all subsequent amendments were reviewed and found to be adequate. Esmolol hydrochloride has a chiral center in the 2 position of the propoxy chain, hence the molecule exists as two enantiomers, (b) (4)

(b) (4) The same DMF is referenced for esmolol hydrochloride (b) (4)

Drug Product: The product will be marketed in two strengths, 2500mg/250mL and 2000mg/100mL, as a ready to use injection in infusion bags. The excipients in the formulation include sodium acetate trihydrate and glacial acetic acid (b) (4) ethanol and propylene glycol (b) (4) sodium hydroxide as pH adjuster, and water for injection (b) (4) All excipients are compendial and below the limits in the Inactive Ingredient database for this route of administration. The manufacturing process included (b) (4)

(b) (4) The Applicant has provided twelve months of stability data for three registration batches of each strength at long term (25°C/40%RH) and six months at accelerated (40°C/15%) conditions. Statistical analysis of the stability data has been performed by the Office of Biostatistics. Based on available stability data, an eighteen month shelf-life has been recommended for the 2500mg/250mL product and a twenty four month shelf-life has been recommended for the 2000mg/100mL product.

Facilities review/inspection: The drug substance and drug product manufacturing sites were submitted for inspection and the current overall Office of Compliance recommendation is “Acceptable”.

4. Nonclinical Pharmacology/Toxicology

The reviewer recommended approval based on the results of the Ames test which demonstrated a lack of genotoxicity of the compound. No other tests were required of the Applicant.

5. Biopharmaceutics

The reviewer recommended approval based on a review of the biowaiver request. The pH and osmolality differences between the listed drug product and the proposed product were determined to be acceptable. The reviewer states that “Although the Delta difference in osmolality results are about 200 mOsm/kg using Freezing Point method and about 100 mmol/kg using Vapor Pressure method, the hemolysis in human whole blood study confirmed that the proposed product does not cause hemolysis compared to the positive control Triton X-100. Therefore, the differences in osmolality determination between the two methods (Freezing Point and Vapor Pressure) are not considered significant”. It was concluded that a biowaiver could be granted.

6. Product Quality Microbiology

The reviewer recommended approval from a quality microbiology perspective with no pending issues. The description and validation of the (b) (4) process was determined to be adequate. It was concluded that the validation studies support the ability of the sterilization cycle to provide product (b) (4) to a sterility assurance level of (b) (4). The endotoxin and sterility methods for release testing of the product were also deemed to be adequate. The integrity of the container closure over the shelf-life of the product was established by appropriate testing in the stability program. The original labeling statement concerning directions for use in the Package Insert, “Once drug has been withdrawn, bag should be used within 24 hours, discarding any unused portion” was not acceptable in the absence of a microbial study to support the 24 hour room temperature storage limit. This issue was resolved by a revision of the Storage and Handling section of the label to exclude storage of the bag once a bolus of the drug is removed.

7. Clinical/Statistical- Efficacy

N/A

8. Safety

N/A

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

N/A

12. Labeling

No proprietary name was proposed by the Applicant. The submitted labels and labeling for the Dual Port Bag, Overwrap and Carton were reviewed by DMEPA and several revisions were recommended, including deletion of “(b) (4)” for the 10 mg/mL strength, to be consistent with Brevibloc labeling. The revised labels and labeling were deemed acceptable by DMEPA.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

All primary reviews of this application recommended approval and I concur with the reviewers. Esmolol Hydrochloride Premixed Injection may be approved with a shelf-life of 18 and 24 months at room temperature for the 10mg/mL and 20 mg/mL strengths, respectively.

- Risk Benefit Assessment

This is a 505(b)(2) application for esmolol hydrochloride premixed injection which relies on the safety and efficacy established for the marketed product, Brevibloc. Consequently, the risk/benefit of this product is expected to be the same as Brevibloc.

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/s/

KASTURI SRINIVASACHAR
04/04/2014