CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205703Orig1s000

CHEMISTRY REVIEW(S)

NDA 205703

Esmolol HCl Premixed Injection 2500mL/250mL (10mg/mL) Infusion Bag and 2000mg/100mL (20mg/mL) Infusion Bag

HQ Specialty Pharma Group

Pei-I Chu, Ph.D.
Office of New Drug Quality Assessment DPA1
For Division of Cardio Renal Drug Products

Review of Chemistry, Manufacturing, and Controls

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Reference ID: 3461042

Chemistry Review Section

Chemistry Review Data Sheet

1. NDA 205703

2. REVIEW # 1

3. REVIEW DATE: February 26, 2014

4. REVIEWER: Pei-I Chu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	June 28, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	HQ Specialty Pharma Corp
Address:	120 Rt 17, North Ste 130, Paramus, NJ 07652
Representative:	Joseph Pizza
Telephone:	201-857-8290

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

a) Proprietary Name: N.A.
b) Non-Proprietary Name (USAN): Esmolol Hydrochloride
c) Code Name/# (ONDC only):N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: N

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9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Beta 2 receptor inhibitor

11. DOSAGE FORM: Premixed Injection

12. STRENGTH/POTENCY: 2500mg/250mL, 2000mg/100mL

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed
X Not a SPOTS product

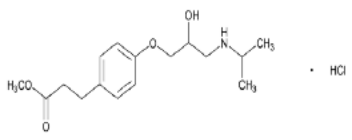
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Benzene-propanoic acid, 4-[2-hydroxy-3- [(1-methyl ethyl)amino]-propoxy]-, methyl ester, hydrochloride, (+/-)

Other Name: (+/-)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate, hydrochloride

Molecular Formula: $C_{16}H_{25}NO_4$, HCl

Molecular Weight: 331.83 g/mol

Structural Formula: 

Reference ID: 3461042

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		1	adequate	11/15/2013	
	III			4			
	III			1	adequate	11/10/2013	
	III			1	adequate	1/30/2014	
	III			1	adequate	1/30/2014	
	II			1	adequate	03/21/2013	
	III			3	adequate	04/01/2013	
	III			1	adequate	11/17/2013	

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	113913	Commercial

Reference ID: 3461042

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	
EES	Acceptable	9/20/2013	Office of compliance
Pharm/Tox	Acceptable	8/30/2013	Philip Gatti
Biopharm	NA	NA	NA
LNC	NA	NA	NA
Methods Validation	NA		NA
OPDRA	NA	NA	NA
DMEPA	Pending	02/25/2014	Loretta Holmes
EA	NA	NA	NA
Microbiology	Pending		Denise Miller

The Chemistry Review for NDA 205703

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 205703 has been reviewed for the chemistry, manufacturing, and controls section. The applicant referenced DMF (b) (4) for the drug substance information. This DMF and all subsequent amendments have been reviewed and found to be adequate. This review covers the CMC information provided for the drug product. The Office of Compliance has determined that the drug substance, drug product and packaging facilities are acceptable. This NDA is recommended for approval from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

The product will be marked 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) and 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. (b) (4) manufactured the pilot batches and the same facility will be used for commercial batches. The manufacturing process included (b) (4) The proposed commercial batch size is (b) (4) the registration batch ((b) (4) L for the 2500mg/250mL product and (b) (4) L for the 2000mg/100mL bags). The applicant has provided twelve-months of stability data for three registration batches of each strength at long term (25ºC/40%RH) and six- months accelerated (40ºC/15%) conditions. Statistical analysis of the stability data has been performed by 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/mL product.

Drug Substance

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Esmolol hydrochloride drug substance is a white to off-white, odorless crystalline (b) (4). The drug substance is freely soluble in water, (b) (4). Its melting point is between 89 ºC -93ºC. Esmolol hydrochloride has a chiral center in the 2 position of the propoxy chain, hence the molecule exists as two enantiomers, (b) (4) and (b) (4) (b) (4). The racemate form of esmolol was selected for development. No evidence of polymorphism has been found. The drug substance is manufactured by (b) (4), as described in the referenced DMF (b) (4). This DMF is referenced for both the esmolol product and the reference drug; the reference drug's manufacturer, Baxter, also sourced esmolol hydrochloride from (b) (4). In addition to the USP requirements, residual solvents, microbial count and bacterial endotoxin tests are performed for release testing. A retest date of (b) (4) months has been established based on the stability data provided in DMF (b) (4).

B. Description of How the Drug Product is Intended to be Used

For supraventricular tachycardia (SVT), the optional loading dose is 500 mcg per kg infused over one minute and then 50 mcg per kg per minute for the next 4 minutes and a maximum of 200 mcg per kg per minute. For perioperative tachycardia and hypertension, the optional loading dose is 500 mcg per kg infused over one minute and then 50 mcg per kg per minute for gradual control and adjusted to a maximum of 200 mcg per kg per minute for tachycardia or 300 (hypertension) mcg per kg per minute.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for approval from the perspective of chemistry, manufacturing and controls.

II. Administrative

A. Reviewer's Signature

Pei-I Chu, Ph.D.

B. Endorsement Block

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Kasturi Srinivasachar, Ph.D.
Chemistry Branch Chief:	Olen Stephens, Ph.D.
Chemistry Project Manager :	Yvonne Knight

C. CC Block

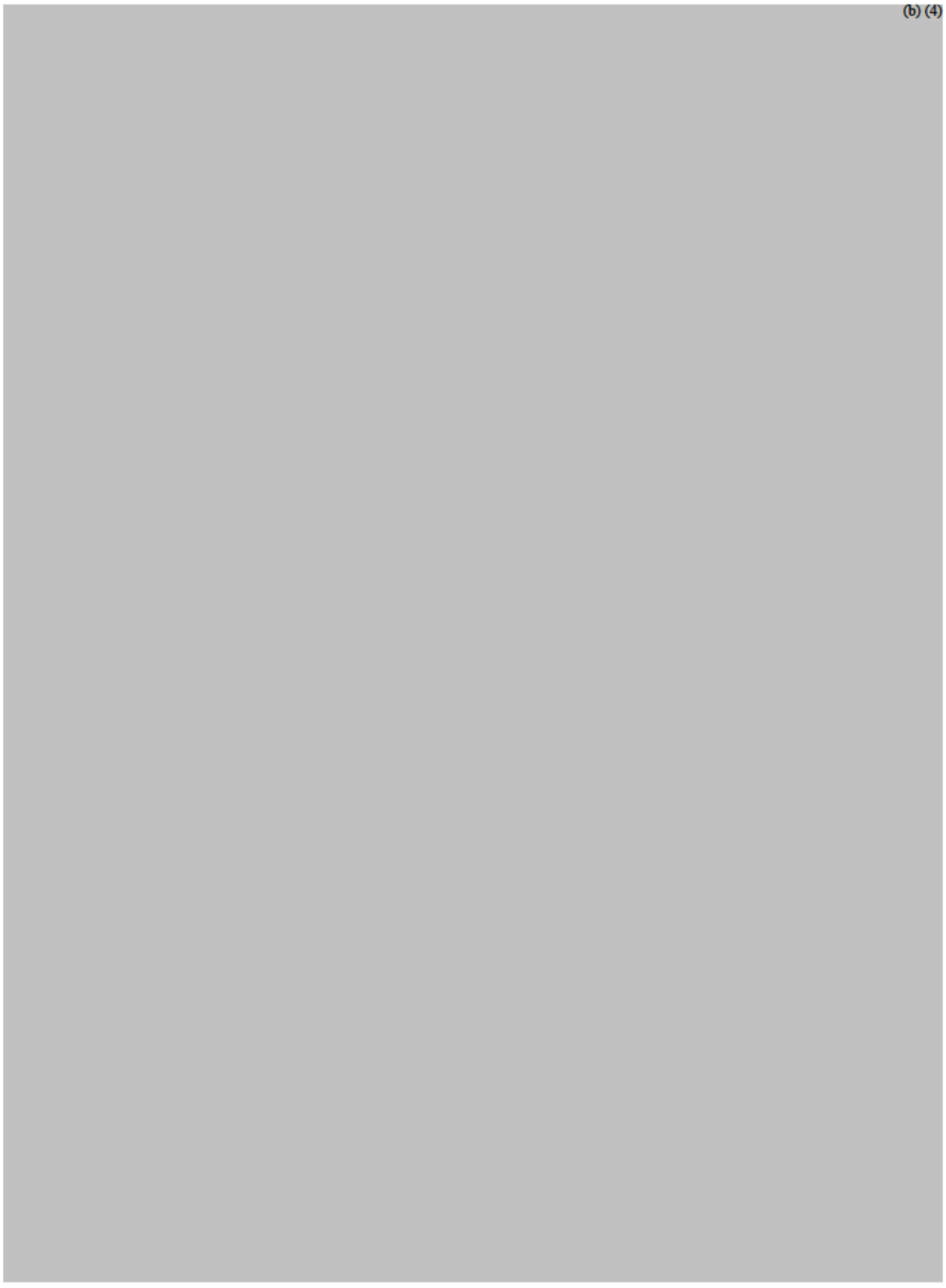
Orig. NDA-205703

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

(b) (4)

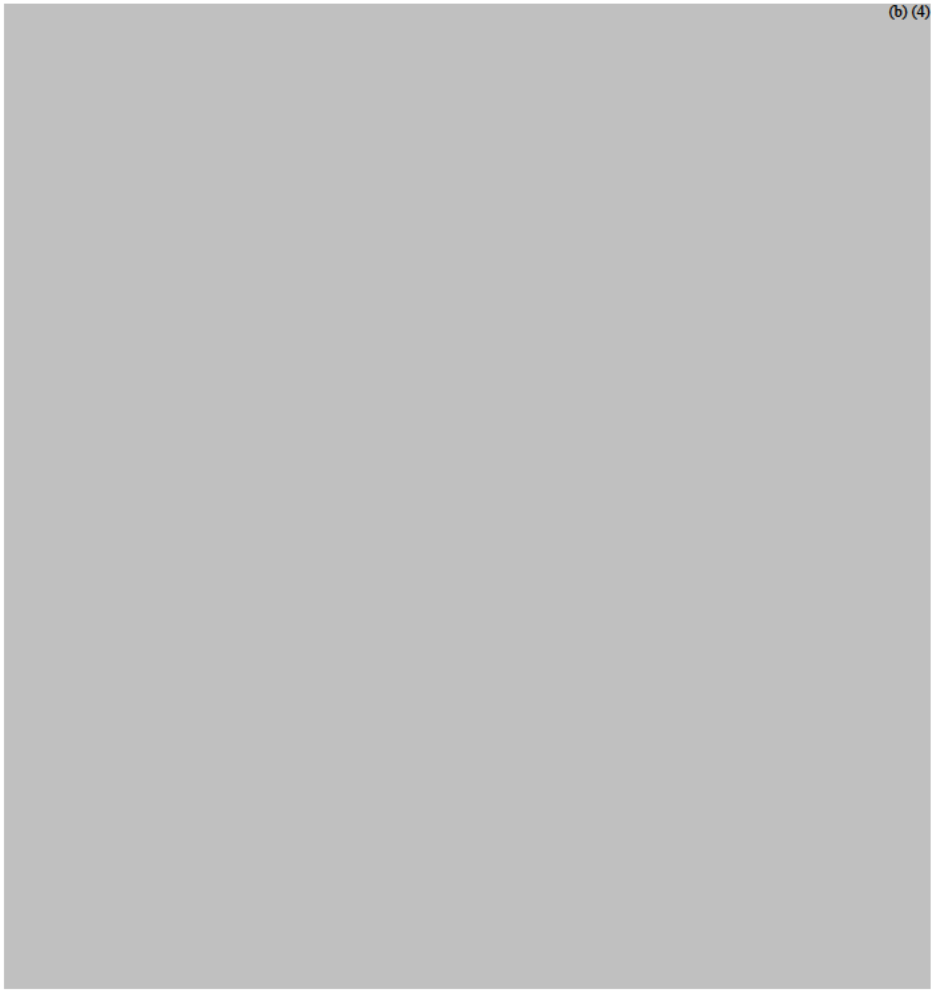
A. Labeling & Package Insert

Representative Overwrap label for the 10mg/mL product is shown below:



Reference ID: 3461042

Representative label for the 10mg/mL dual port bag is shown below:



Representative carton label for the 10mg/mL product:

How Supplied/Storage and Handling

Esmolol Hydrochloride (b) (4) Premixed Injection 2500 mg/250 mL (10 mg/mL) and Esmolol Hydrochloride DOUBLE STRENGTH Premixed Injection 2000 mg/100 mL (20 mg/mL) is available in a ready-to-use dual port bag with an aluminum overwrap.

Each bag is for single-patient use only and does not contain any preservatives. It is advised that once drug has been withdrawn from Esmolol Hydrochloride Premixed Injection, the bag should be used within 24 hours, discarding any unused portion.

Esmolol Hydrochloride Premixed Injection is not compatible with Sodium Bicarbonate (5%) solution (limited stability) or furosemide (precipitation).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

16.2 Storage

Store at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from freezing. Avoid excessive heat.

Each bag contains no preservative. Once drug has been withdrawn from ready-to-use bag, the bag should be used within 24 hours, with any unused portion discarded.

EVALUATION: NOT ADEQUATE. The labels contains the following required information: product name, Rx only; NDC number, strength, and the declaration of the quantity of drug solution per bag, manufacturer's name and address, lot number; bar code, storage condition and expiration date. However, the applicant stated that after initial withdrawal of the product, the bag should be used within 24 hrs. What is the basis for the sponsor's statement?

12/05/2013 QUESTION: Section 16.2 (Storage and Handling) of the proposed package insert states the (b) (4) Provide a microbial study to support the 24 hour room temperature storage limit. The study may be either the USP <51> Antimicrobial Effectiveness Testing procedure and acceptance criteria or a microbial proliferation study designed to demonstrate that the drug product does not support microbial growth during the proposed holding period. If a microbial proliferation study is performed, then the report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product withdrawal from the primary container. It is generally accepted that growth is evident when the population increases more than 0.5 Log10 (based on the statistical sensitivity of the assay), or when trended data indicate initiation of growth. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. The USP <51> is quoted as a reference of the organisms to be used in the microbial proliferation study and not for the test procedure or acceptance criteria described in the chapter. In lieu of a study, the recommended storage limit would be 4 hours at room temperature or not more than 12 hours refrigerated. What is the basis for the statement in section 16.2 (Storage and Handling) of the package insert that after initial withdrawal of the drug the bag should be used within 24 hrs?

RESPONSE: A microbial proliferation study was conducted. The Microbiology reviewer has evaluated the results and will recommend shortening the storage period.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The applicant requested categorical exclusion for esmolol hydrochloride. However, the EIC calculation was not provided.

EVALUATION: NOT ADEQUATE. The applicant should provide estimated introduction concentration (EIC) calculation to request categorical exclusion.

12/05/2013 QUESTION: Provide estimated introduction concentration (EIC) calculation to justify categorical exclusion.

RESPONSE: In accordance with 21 CFR 25.31(a), the approval of this 505(b)(2) NDA will not increase the amount of active moiety. Rather, the proposed product will act as a generic substitution for the current branded product- Brevibloc.

EVALUATION: ADEQUATE.

Chemistry Review Section

Establishment Evaluation Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205703/000	**Sponsor:**	HQ SPCLT PHARMA
Org. Code:	110		120 RT 17 NORTH STE 130
Priority:	5		PARAMUS, NJ 07652
Stamp Date:	28-JUN-2013	**Brand Name:**	ESMOLOL HCL PREMIXED INJ 2500MG/250ML (1
PDUFA Date:	28-APR-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	ESMOLOL HCL PREMIXED INJ 2500MG/250ML (1
District Goal:	27-FEB-2014	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION, INJECTION; ESMOLOL HYDROCHLORIDE; 2500MG/250ML (10MG/ML) 002; SOLUTION, INJECTION; ESMOLOL HYDROCHLORIDE; 2000MG/100ML (20MG/ML)	

FDA Contacts:	P. CHU	Prod Qual Reviewer	3017963887
	T. BOUIE	Product Quality PM	3017961649
	R. FORTNEY	Regulatory Project Mgr	3017961068
	K. SRINIVASACHAR	Team Leader	3017961760

Overall Recommendation: ACCEPTABLE on 20-SEP-2013 by R. WITTORF ()

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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FINAL RECOMMENDATION: This NDA is recommended for **APPROVAL** from the perspective of chemistry, manufacturing and controls.

Reference ID: 3461042

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

/s/

PEI-I CHU
02/26/2014

OLEN M STEPHENS
02/26/2014