# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205703Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 205-703 | **Reviewer:**<br>Houda Mahayni, Ph.D. | |
| **Division:** | DCRP | | |
| **Applicant:** | HQ Specialty Pharma Corp | **Team Leader:**<br>Angelica Dorantes, Ph.D. | |
| **Trade Name:** | -- | **Acting Supervisor:**<br>Richard T. Lostritto, Ph.D. | |
| **Generic Name:** | Esmolol HCl Premixed Injection | **Date Assigned:** | June 28, 2013 |
| **Indication:** | -Control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter and control of heart rate in noncompensatory sinus tachycardia.<br>-Control of perioperative tachycardia and hypertension | **Date of Review:** | March 17, 2014 |
| **Formulation/strength** | Premixed Injection/(2500 mg/250 mL) and (2000 mg/100 mL) | | |
| **Route of Administration** | Injectable | | |

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

| SUBMISSION DATE | GRMP DATE | PDUFA DATE |
|---|---|---|
| June 28, 2013 | March 24, 2014 | April 28, 2014 |

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|---|---|
| **Type of Submission:** | 505 (b) (2) |
| **Key review points** | Evaluation of the Biowaiver request |

**TABLE OF CONTENTS**

# I) EXECUTIVE BIOPHARMACEUTICS SUMMARY

## *Background:*

Brevibloc® (Esmolol Hydrochloride) is a cardio-selective beta-adrenergic receptor blocking agent administered intravenously and has a very short duration of action (elimination half-life is approximately 9 minutes). It is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short-term control of ventricular rate with a short-acting agent is desirable. It is also indicated in non-compensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. Brevibloc® brand was originally developed and registered by Du Pont Pharma. Du Pont Pharma sold its rights to Ohmeda PPD Inc. in 1993. Ohmeda PPD Inc. was purchased by Baxter in 1998.

In December 1986, FDA approved the original new drug application (NDA 019386) with two presentations: 10 mg/mL in 10 mL vial (ready-to-use, non-isotonic) to be administered by bolus and infusion; and 250 mg/mL in 10 mL ampoules (co-solvent concentrate) to be diluted before use.

In 2001 and 2003, Baxter Healthcare Corporation introduced a patented, Brevibloc® Premixed Injection in Single and Double Strength (Esmolol HCl 10 mg/mL and 20 mg/mL, respectively) in an Intravia® plastic bag with an isotonic adjusting agent (sodium chloride) through supplements to the application. The original presentation (ready-to-use vial) was re-formulated into a larger volume infusion with sodium chloride as isotonic agent.

On June 28, 2007, Baxter informed the FDA that the company had ceased the manufacture and distribution of Brevibloc® (esmolol HCl) Injection, 250 mg/mL, 10-mL ampoule due to serious adverse events via medication errors. FDA ruled that the Brevibloc® (esmolol HCl) Injection, 250 mg/mL, 10-mL ampoule formulation was withdrawn for reasons of safety, due to medication errors, and would not accept or approve ANDAs that refer to Brevibloc (esmolol HCL) Injection, 250mg/mL, 10-mL ampoule.

***Submission:***

The proposed drug product, 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 submitted as a New Drug Application (NDA) under Section 505 (b) (2) of the FDC Act. The Listed Drug Product (LDP) is Breviloc® Premixed Injection in Single and Double Strength (Esmolol HCl 10 mg/mL and 20 mg/mL, respectively) by Baxter Healthcare Corporation.

Esmolol Hydrochloride is freely soluble in water. Both dosage strengths of the proposed drug product, 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), are a ready to infuse solution filled in [redacted] bags, referred to as [redacted]™ bags. The proposed formulations contain the same active but different inactive ingredients than the Listed Drug Product.

The proposed product, Esmolol Hydrochloride Premixed Injections of 10 mg/mL and 20 mg/mL in flexible plastic bags, has formulation matrix as the discontinued Brevibloc® 250 mg/mL, 10-mL presentation when admixed with WFI. Therefore, the proposed formulation and the LD have different osmolality. The proposed formulations are not iso-osmotic as compared to the LD. The Applicant stated that presentations of Esmolol admixtures with different diluents have been marketed with osmolalities ranging from 659 to 1200 mOsml/L, and have shown to be safe.

The development batches of the proposed drug product were manufactured at [redacted] which is the same facility that will be used to manufacture the commercial product.

***Review:***

This review is focused on the evaluation of the data supporting the acceptability of the biowaiver request.

It is noted that FDA agreed in the written responses provided to the Applicant under PIND 113913 in a letter dated January 18, 2012, that the different excipients and the osmolalities will not require additional clinical studies to support the approval of the proposed Esmolol HCl Premixed Injection NDA (see FDA's answer to question (1b) in the meeting written responses). Furthermore, FDA agreed that it is appropriate to request a waiver per 21 CFR §320.22 (b) (1). (Refer to the FDA's answer to question (3d) in the meeting written responses). Attached is the link to the meeting written responses: \\cdsesub1\evsprod\NDA205703\0000\m1\us\16-meetings\correspondence-regarding-meetings

## II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed NDA 205-703 for Esmolol Hydrochloride [redacted] Premixed Injection 2500 mg/250 mL (10 mg/mL) and Esmolol Hydrochloride Double Strength Premixed Injection 2000 mg/100 mL (20 mg/mL) and found the biowaiver request acceptable. Therefore, the biowaiver is granted.

From the Biopharmaceutics perspective, NDA 205-703 is recommended for APPROVAL.

**Houda Mahayni, Ph. D.**
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Angelica Dorantes, Ph.D.**
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

**cc: DARRTS/Lostritto**

# III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

## A) GENERAL ATTRIBUTES

***a. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility)?***

The Applicant reported that Esmolol Hydrochloride is freely soluble in water.

***b. What is the route of administration? How is the product being administered?***

The proposed product is an injectable to be administered intravenously. The product is formulated in a ready-to-use, (b) (4), flexible plastic bag with no need for further dilution before administration.

***c. Does the drug product include a delivery device?***

No.

## B) DRUG PRODUCT FORMULATION

***d. What is the formulation?***

The Applicant proposed the following two dosage strengths:

- Esmolol Hydrochloride (b) (4) Premixed Injection 2500 mg/250 mL (10 mg/mL)
- Esmolol Hydrochloride Double Strength Premixed Injection 2000 mg/100 mL (20 mg/mL).

Table 1 and Table 2 list the components and composition of each strength of Esmolol Hydrochloride Premixed Injections on a mg/mL and container basis.

**Table 1: Components and Composition of Esmolol Hydrochloride Premixed Injection (b) (4) 2500 mg/250 mL (10 mg/mL)**

| Name of Ingredients | Composition | | |
|---|---|---|---|
| | Label Claim | mg /mL | mg per 250 mL container |
| Esmolol HCl | 10 mg/mL | (b) (4) mg/mL[1] | (b) (4) |
| Sodium Acetate trihydrate | 0.68 mg/mL | 0.68 mg/mL | 170 |
| Glacial Acetic Acid | (b) (4) mg/ mL | (b) (4) mg/ mL | (b) (4) |
| Ethanol[2] | (b) (4) mg/mL | (b) (4) mg/mL | |
| Propylene Glycol[3] | 10 mg/mL | 10 mg/mL | 2500 |
| Sodium Hydroxide | As Needed | As Needed | As Needed |
| WFI | QS | QS | QS |
| **Total** | **1 mL** | **1 mL** | **250 mL** |

[1] based on experimental batches there is a (b) (4) % loss during (b) (4) therefore (b) (4) % is added to batch
[2]Ethanol was corrected for density (density= (b) (4) g/mL)
[3]Propylene glycol was corrected for density( density = (b) (4) g/mL)

**Table 2: Components and Composition of Esmolol Hydrochloride Premixed Injection Double Strength 2000 mg/100 mL (20 mg/mL)**

| Name of Ingredients | Composition | | |
|---|---|---|---|
| | Label Claim | mg /mL | mg per 100 mL container |
| Esmolol HCl | 20 mg/mL | (b) (4) mg/mL[1] | (b) (4) |
| Sodium Acetate trihydrate | 0.68 mg/mL | 0.68 mg/mL | 68 |
| Glacial Acetic Acid | (b) (4) mg/ mL | (b) (4) mg/ mL | (b) (4) |
| Ethanol[2] | (b) (4) mg/mL | (b) (4) mg/mL | (b) (4) |
| Propylene Glycol[3] | 10 mg/mL | 10 mg/mL | 1000 |
| Sodium Hydroxide | As Needed | As Needed | As Needed |
| WFI | QS | QS | QS |
| **Total** | **1 mL** | **1 mL** | **100 mL** |

[1]based on experimental batches there is a (b) (4)% loss during autoclaving; therefore (b) (4)% is added to batch
[2]Ethanol was corrected for density (density= (b) (4) g/mL)
[3]Propylene glycol was corrected for density( density = (b) (4) g/mL)

***e. What are the highlights of the drug product formulation development?***

The proposed formulations have the same formulation matrix as the discontinued Brevibloc® 250 mg/mL, 10-mL presentation when admixed with WFI.

The drug product is an aqueous solution. The proposed formulations were designed to have among other attributes a pH of 4.5-6.5, and an apparent osmolality of 350-500 mOsm/kg.

**C) SUPPORTIVE INFORMATION**

***f. What data are available to support the approval of the proposed product?***

The Applicant conducted two test methods to compare the osmolality of the proposed product to the LD: *USP<785> Freezing Point method, and USP <785> Vapor Pressure method*. The osmolality results for each of the strengths (proposed product vs. LD) using the Freezing Point method are shown in Table 3 and Table 4, respectively.

**Table 3: Osmolality Results of the Proposed Product Using the USP <785> Freezing Point Method**

| Sample ID | DESCRIPTION | LOT # | CLAIM | RESULT |
|---|---|---|---|---|
| 001 | Esmolol HCl 2500mg/250mL | 2R008 | Report Result | 405 mOsm/kg |
| 002 | Esmolol HCl 2000mg/100mL | 2R005 | Report Result | 454 mOsm/kg |

**Table 4: Osmolality Results of the LD Using the USP <785> Freezing Point Method**

| Sample ID | DESCRIPTION | LOT # | CLAIM | RESULT |
|---|---|---|---|---|
| 001 | Brevibloc Premixed Injection | C834077 | Report Result | 299 mOsm/kg |
| 002 | Brevibloc Double Strength Premixed Injection | C844779 | Report Result | 300 mOsm/kg |

And, the osmolality results obtained for each of the strengths (proposed product vs. LD) using the Vapor Pressure method is shown in Table 5 and Table 6, respectively.

**Table 5: Osmolality Results of the Proposed Product Using the USP <785> Vapor Pressure Method**

| Sample ID | DESCRIPTION | LOT # | CLAIM | RESULT |
|---|---|---|---|---|
| 001 | Esmolol HCl 2500mg/250mL | 2R008 | Report Result | 184 mmol/kg |
| 002 | Esmolol HCl 2000mg/100mL | 2R005 | Report Result | 239 mmol/kg |

**Table 6: Osmolality Results of the LD Using the USP <785> Vapor Pressure Method**

| Sample ID | DESCRIPTION | LOT # | CLAIM | RESULT |
|---|---|---|---|---|
| 001 | Brevibloc Premixed Injection | C834077 | Report Result | 277 mmol/kg |
| 002 | Brevibloc Double Strength Premixed Injection | C844779 | Report Result | 275 mmol/kg |

Furthermore, the Applicant performed a study to determine the human hemolytic potential for the proposed product as compared to the LDP. Three products (Brevibloc double strength, Esmolol HCl, or Esmolol HCl (Mylan)) were assessed against the positive control Triton X-100 for their ability to cause hemolysis in human whole blood. According to the Applicant, none of the three products caused any hemolysis. The results are shown in Table 7. Also, the link to the study report is: \\cdsesub1\evsprod\NDA205703\0007\m4\42-stud-rep\423-tox\4237-other-tox-stud\42371-antigen

**Table 7: Hemolysis Data**

| Sample | Test Conc. | % Lysis 1st replicate | % Lysis 2nd replicate | % Lysis 3rd replicate | Mean % Lysis | SD |
|---|---|---|---|---|---|---|
| 0.9% NaCl solution (vehicle) | - | -0.1% | -0.2% | -0.2% | -0.2% | 0.04% |
| Triton X-100 | 0.1 % | 17.9% | 19.7% | 16.2% | 17.9% | 1.7% |
| Triton X-100 | 1% | 86.1% | 92.3% | 93.5% | 90.6% | 4.0% |
| **Brevibloc Double Strength** | 10 % | -0.1% | -0.1% | -0.1% | -0.1% | 0.01% |
| **Esmolol HCl** | 10 % | -0.1% | 0.0% | -0.1% | -0.1% | 0.02% |
| **Esmolol HCl (Mylan)** | 10 % | -0.1% | -0.1% | -0.1% | -0.1% | 0.03% |

***Reviewer's Note:***
*The osmolality results show that the proposed product has comparable osmolality to the listed drug product using the Vapor Pressure method. Furthermore, there was no evidence of hemolysis comparing the proposed product to the listed drug product at 10% concentration.*

***g. Does the Applicant rely on the safety and/or efficacy of a Listed Drug product?***
Yes, the Applicant relies on FDA's previous findings of safety and efficacy of the clinical studies described in NDA-019386 Brevibloc Premixed® Injection as the sole source of clinical data to support the Applicant's Esmolol HCl Premixed Injection.

***h. Was a bioequivalence study conducted? If yes, is a Biopharmaceutics Review needed for the submission?***
No, the Applicant requested a biowaiver.

**D) BIOWAIVER**

***i. Is there a waiver request for the submission of in vivo BA/BE data (biowaiver)?***
Yes, FDA stated in the PIND letter dated January 18, 2012 that bioequivalence studies were not required. Also, in the same letter FDA agreed that it is appropriate to request a waiver for the requirements of evidence of in vivo bioavailability or bioequivalence in accordance with the 21 CFR 320.22(b) (1).

The proposed Esmolol Hydrochloride Premixed Injection drug product formulations (subject of this NDA) contain the same active ingredients, same route of administration and indications as the LDP, Brevibloc® Premixed Injection of Baxter. However, the inactive ingredients of the proposed product are not the same as compared to the LDP. However, the inactive ingredient in the proposed product are similar but at lower concentrations than the discontinued product.

***j. What is the purpose of the biowaiver request?***
To waive evidence to demonstrate in-vivo biavailability/ bioequivalence to the LDP, as the proposed product does not contain the same inactive ingredients as the LDP.

***k. What information supports the biowaiver request?***

The Applicant provided the following statements as the basis to support the biowaiver request:

1. *The active ingredient for the proposed drug product is the same as that of the listed drug product.*
2. *The route of administration, dosage form and strength of the proposed drug product are the same as those of the listed drug product when administered.*
3. *Composition of the proposed product differs from that of the LDP listed herein and therefore it is not eligible to submit as an ANDA under Section 505(j) of the FDC Act*
4. *The labeling for the proposed drug product is the same as that of the listed drug product, with the exception of those changes outlined in the annotated labeling.*

The main differences in the formulation between the LDP and proposed product are:

- The inactive ingredients ethanol and propylene glycol are present in the proposed product but these ingredients are not present in the LDP.
- The inactive sodium chloride is present in the LDP but not present in the proposed product
- The concentration of acetate buffer is different
- The osmolality are different between the LDP and proposed product

The information that supports the biowaiver request is that the range of pH values between the LDP and proposed product are similar 4.5-5.5 and the range of osmolality 390-490 mOsmol/L.

To support the osmolality of the proposed product, the Applicant conducted a comparison between Brevibloc® Premixed injections and Esmolol Premixed injections using both Freezing Point Depression and Vapor Pressure USP methods. The results indicated that Esmolol Premixed Injections are either hyperosmotic solutions or hypoosmotic solutions relative to Brevibloc® Premixed injections depending on the method used to measure the osmolality.

The Applicant reported that the delta change between the two products using the Vapor Pressure method to measure the osmolality suggests that the solutions are practically similar. However, the Freezing Point method shows a delta change of over 100 mOsmol/kg between the products (LDP and proposed). The Applicant stated that both hyperosmotic solutions and hypoosmotic solution of Esmolol have been marketed for over decades with no impact on safety. Therefore, the osmolality of Esmolol Premixed formulations (depending on the technique: Vapor Pressure, Freezing Point) is not expected to have any impact on safety.

Table 8 shows the results of osmolality studies of Esmolol Hydrochloride Premixed Injections compared with Brevibloc® Premixed Injections (10 and 20 mg/mL).

**Table 8: Summarized results of Osmolality studies of Esmolol Premixed Injections compared with Brevibloc® Premixed Injections (10 and 20 mg/mL)**

| Sample Description | Lot Numbers | Osmolality Results | Delta Difference |
|---|---|---|---|
| Freezing Point depression | | | |
| Esmolol Premixed Injection, 10 mg/mL | 2R008 | 405 mOsm/kg | 196 mOsm/kg |
| Brevibloc® Premixed Injection, 10 mg/ml | C834077 | 299mOsm/kg | |
| Esmolol Premixed Injection, 20 mg/mL | 2R005 | 454 mOsm/kg | 154 mOsm/kg |
| Brevibloc® Premixed Injection, 20 mg/ml | C844779 | 300 mOsm/kg | |
| Vapor Pressure | | | |
| Esmolol Premixed Injection, 10 mg/mL | 2R008 | 184 mmol/kg | 93 mmol/kg |
| Brevibloc® Premixed Injection, 10 mg/ml | C834077 | 277 mmol/kg | |
| Esmolol Premixed Injection, 20 mg/mL | 2R005 | 239 mmol/kg | 36 mmol/kg |
| Brevibloc® Premixed Injection, 20 mg/ml | C844779 | 275 mmol/kg | |

Additionally, the Applicant later conducted hemolysis study which showed lack of hemolytic potential of the proposed product as compared to the positive control Triton X-100. Here is the link to the study report: \\cdsesub1\evsprod\NDA205703\0007\m4\42-stud-rep\423-tox\4237-other-tox-stud\42371-antigen

***Reviewer's Comment:***
*The pH and osmolality differences between the LDP and the proposed product are acceptable. 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 did 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.*

***l. What is the listed drug product?***
Brevibloc® Premixed Injection in Single and Double Strength (Esmolol HCl 10 mg/mL and 20 mg/mL).

***m. Is the listed drug product an official Listed Drug Product (LDP)?***
Yes.

***n. What is the formulation of the listed drug product?***
Table 9 and Table 10 show the formulation of the LDP for the 10 mg/mL and 20 mg/mL, respectively.

**Table 9: Formulation of the LDP (10 mg/mL)**

| Ingredient | RLD: Brevibloc® Premixed Injection (Label claim) |
|---|---|
| Esmolol HCl | 10 mg/ mL |
| Sodium chloride | 5.9 mg/mL |
| Sodium Acetate Trihydrate | 2.8 mg/mL |
| Glacial Acetic Acid | 0.546 mg/mL |
| Ethanol | NA |
| Propylene Glycol | NA |
| Sodium Hydroxide | As required |
| Water for Injection | Q.S. (Quantity Sufficient) |

**Table 10: Formulation of the LDP (20mg/mL)**

| Ingredient | RLD: Brevibloc® Premixed Injection (Label claim) |
|---|---|
| Esmolol HCl | 20 mg/mL |
| Sodium chloride | 4.1 mg/mL |
| Sodium Acetate Trihydrate | 2.8 mg/mL |
| Glacial Acetic Acid | 0.546 mg/mL |
| Ethanol | NA |
| Propylene Glycol | NA |
| Sodium Hydroxide | As required |
| Water for Injection | Q.S. (Quantity Sufficient) |

***o. Are there any differences in the formulations of the proposed and the listed drug product?***

Yes, there are differences in the formulations of the proposed and the LDP.

FDA sent the following information request to the Applicant in the Filing Communication dated September 5, 2013:

*Provide a comparative table for each of the proposed strengths listing the components and composition of the LDP and the proposed product to include the amount of active ingredient, as the provided comparative tables in the submission listed only the inactive ingredients.*

The Applicant responded on September 18, 2013, providing the following two tables which show that the excipients are different between the LDP and the proposed product as shown in Table 11 and Table 12.

The differences in the formulation between the LDP and the proposed product are in the excipients used as shown in Table 11 and Table 12. The proposed product contains ethanol and propylene glycol. However, the LDP does not contain ethanol and propylene glycol. Also, sodium chloride is present in the LDP but not in the proposed product. Additionally, the acetate buffer concentration is different.

**Table 11: Excipients of the LDP (10 mg/mL) as Compared to the Proposed Product**

| Ingredient | RLD: Brevibloc® Premixed Injection (Label claim) | Proposed Product: Esmolol HCl Premixed Injection (Label claim) |
|---|---|---|
| Esmolol HCl | 10 mg/ mL | 10 mg/ mL |
| Sodium chloride | 5.9 mg/mL | NA |
| Sodium Acetate Trihydrate | 2.8 mg/mL | 0.68 mg/mL |
| Glacial Acetic Acid | 0.546 mg/mL | (b) (4) mg/ mL |
| Ethanol | NA | (b) (4) |
| Propylene Glycol | NA | 10 mg/mL |
| Sodium Hydroxide | As required | As required |
| Water for Injection | Q.S. (Quantity Sufficient) | Q.S. (Quantity Sufficient) |

**Table 12: Excipients of the LDP (20 mg/mL) as Compared to the Proposed Product**

| Ingredient | RLD: Brevibloc® Premixed Injection (Label claim) | Proposed Product: Esmolol HCl Premixed Injection (Label claim) |
|---|---|---|
| Esmolol HCl | 20 mg/mL | 20 mg/mL |
| Sodium chloride | 4.1 mg/mL | NA |
| Sodium Acetate Trihydrate | 2.8 mg/mL | 0.68 mg/mL |
| Glacial Acetic Acid | 0.546 mg/mL | (b) (4) mg/ mL |
| Ethanol | NA | (b) (4) |
| Propylene Glycol | NA | 10 mg/mL |
| Sodium Hydroxide | As required | As required |
| Water for Injection | Q.S. (Quantity Sufficient) | Q.S. (Quantity Sufficient) |

***Reviewer's Comment***: *The current formulation contains the same excipients as the discontinued product.*

***p. Do the proposed or listed drug products contain excipients that can affect the disposition and/or distribution of the drug?***

Although there are slight differences in osmolality, there is no evidence that it may have an effect on the disposition and/or distribution of the drug.

FDA sent Information Request on December 5, 2013 which included the following question:

*The osmolality of the drug product was high (320 -450 mOsmol/L for 2500mg/250mL, 440-500 mOsmol/L). Conduct hemolysis assay to demonstrate that it will not cause hemolysis when injected into humans.*

The Applicant responded providing the following information:

*The osmolality specification for the proposed product is not high. The discontinued Brevibloc (250mg/ mL) when admixed and infused with different diluents were found to have osmolalities ranging from 659 to 1200 mOsm/L. [Reference: West, Donald B., et al. "Stability of esmolol hydrochloride in 5% dextrose injection." Am J Health-Syst Pharm 52 (1995): 716-718, and Trissel, Lawrence. Handbook on Injectable Drugs, 15th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2009.]. A study was conducted testing osmolality of Brevibloc and the proposed product by two separate methods per USP <785>: freezing point depression and vapor pressure. Results show that the freezing point depression is affected by* (b) (4) *(our proposed*

*product contains total* (b) (4) *). Freezing point technique is used as a control to ensure organic specifications added are within specification. Further, the innovator conducted a human blood compatibility study on formulations ranging from 10-70% propylene glycol and 10-60% ethanol. Results show no hemolysis occurred to formulations tested. Nonetheless, a hemolysis assay study is being conducted. As agreed with Y. Knight on December 13, 2013, the results will be provided upon completion and submitted no later than mid-February 2014.*

The referenced hemolysis study was submitted on January 30, 2014 and attached here: \\cdsesub1\evsprod\NDA205703\0007\m4\42-stud-rep\423-tox\4237-other-tox-stud\42371-antigen

The referenced innovator study which was conducted using a human blood to assess the compatibility of formulations ranging from 10-70% propylene glycol and 10-
60% ethanol with human blood is attached here:
\\cdsesub1\evsprod\nda205703\0006\m4\42-stud-rep\423-tox\4237-other-tox-stud\42371-antigen\4237-hemolysis.pdf

***q. What is the difference in pH, administered volume, and osmolarity of the proposed and the listed drug product?***

The proposed product contains ethanol, propylene glycol. The LDP formulation does not contain ethanol and propylene glycol. However, ethanol and propylene glycol were contained in the discontinued Brevibloc (Esmolol HCl) Injection 250 mg/mL in 10 mL ampoule.

The LDP premixed injections have two formulations: 2000mg/100 mL and 1000 mg/100 mL. The proposed product has a higher volume (and 2000 mg/100 mg and 2500 mg/250mL). However, the concentration of active in the proposed product is the same as in the LD (10 mg/mL and 20 mg/mL).

The pH ranges of the LDP formulations (10 mg/mL and 20 mg/mL) are 4.5-5.5. The target pH ranges of the proposed product are 4.5-6.5.

The apparent osmolality of LDP is 255-345 mOsmol/L for the 20 mg/mL formulation and 270-330 mOsmol/L for the 10 mg/mL formulation. The target apparent osmolality of the proposed product is 440-500 mOsmol/L for the 20 mg/mL formulation and 320-450 mOsmol/L for the 10 mg/mL formulation.

The proposed product's apparent pH and apparent osmolality release specifications are:

- Esmolol Hydrochloride (b) (4) Premixed Injection 2500 mg/250 mL (10 mg/mL) is set to 4.9-5.2 pH units and 390-430 mOsmol/L, respectively.
- Esmolol Hydrochloride Double Strength Premixed Injection 2000 mg/100 mL (20 mg/mL) is set to 4.9-5.2 pH units and 440-490 mOsmol/L, respectively.

The Applicant attributed the hypertonicity (apparent osmolality range 390-490 mOsmol/L) to the analytical procedure and the [redacted] (b) (4) present, as the true osmolality is only a function of the Esmolol concentration and the buffer system.

***Reviewer's Comment:***

*The current formulation contains the same excipients as the discontinued product. The concentration of the discontinued product was: Esmolol HCl (250mg/mL), sodium acetate trihydrate [redacted] (b) (4), glacial acetic acid [redacted] (b) (4) ethanol [redacted] (b) (4) and propylene glycol [redacted] (b) (4). The concentrations of the same excipients in the proposed product are much lower than those same excipients in the discontinued product. Therefore, these excipients would not be expected at these lower concentrations to affect the disposition and/or distribution of the drug.*

***r. Are the CFR requirements for granting a biowaiver met? If not, are the provided justification and supportive data appropriate?***

Yes.

***s. Is the overall information supporting the biowaiver request acceptable?***

Yes.

***t. Is the biowaiver granted?***

Yes.

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/s/

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