

## Clinical Pharmacology and Biopharmaceutics Review

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<b>NDA 19-386</b>		<b>SUBMISSION DATES</b>
	S-026	MAY 29, 2003
		JUNE 30, 2003
		JULY 8, 2003
		JULY 16, 2003
	SE5-026 BB	JULY 29, 2003
<b>DRUG NAME:</b> esmolol, Brevibloc®		
<b>STRENGTH AND FORMULATION:</b> 10, 20, 250 MG/ML		
<b>SPONSOR:</b> Baxter		
<b>REVIEWER:</b> B. Nhi Nguyen, Pharm.D.		
<b>TYPE OF SUBMISSION:</b> sNDA, efficacy supplement in response to pediatric written request		

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### 1 Executive Summary

This supplement is a response to the pediatric written request (WR) sent September 30, 1999 and amended on March 6, 2000. With respect to clinical pharmacology, the WR specifies that the sponsor collect pharmacokinetic data in surgical patients ages 6 to 16 years old. Other components of the WR include a dose-ranging efficacy trial in pediatric patients  $\leq 6$  years old following surgery for coarctation of the aorta.

The sponsor conducted two clinical studies for exclusivity. Study 20,015-005 was an open label, single dose pharmacokinetic study in children (2.5 months to  $\sim 7$  years old). Study 20,015-004 was a randomized, parallel, double-blind, efficacy and pharmacokinetic study in newborns to 7 year olds with change in systolic blood pressure (SBP) at 5 minutes as the primary effectiveness endpoint.

The sponsor evaluated the exposure-change in SBP relationship. Regression analysis showed no significant relationship between exposure (dose or concentration) and change in SBP at 5 minutes.

The reviewer assessed the concentration-change in SBP (relative to baseline) relationship in the efficacy study (004) and reviewed the pharmacokinetics of esmolol in pediatric patients in both studies. The reviewer considered the full time course of change in SBP over 15 min (SBP recorded every minute) along with model predicted esmolol arterial concentrations. No clear relationship exists between concentrations and change in SBP, according to a variety of analyses conducted by the reviewer. However, as also noted by the sponsor, there is an exposure-change in heart rate relationship in Study 004.

#### 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has completed the review of esmolol in pediatric patients and recommends the following:

**1. Labeling** - Because of the lack of effectiveness, no information regarding the pharmacokinetics are recommended for the label.

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Division of Pharmaceutical Evaluation I

FT Initialed by Joga Gobburu, Ph.D. \_\_\_\_\_

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