Medical Officer Executive Summary

NDA: 19-386, S-026
Drug Name: esmolol
Trade Name: Brevibloc
Route of administration: IV
Dose strengths: 10, 20, 250 mg/mL
Proposed indications: supraventricular tachycardia; intraoperative and postoperative tachycardia and/or hypertension
Sponsor: Baxter

Reviewer: Shari L. Targum, MD
Pediatric Written requests: 9/30/1999, 3/6/2000
Date Supplement Submitted: 5/29/2003
Date Received by CDER: 5/30/2003
Date Received by Reviewer: 6/5/2003
Filing Meeting: 7/9/2003
Pediatric Exclusivity Board meetings: 7/22/2003, 8/21/2003
Date Review Completed: 10/10/2003

Executive Summary:
This supplement is a response to the pediatric written request sent on the above dates. Two pediatric exclusivity board meetings were held (see above dates) and a decision was subsequently made in favor of exclusivity.

The sponsor submitted two clinical trials: one randomized, double-blind without a placebo control conducted in pediatric patients (0-6 years) undergoing repair of aortic coarctation (20,015-004) and a smaller uncontrolled trial conducted children (2-16 years) with SVT (20,015-005).

Study 20, 015-004 was a randomized, double-blind study comparing efficacy of 3 doses of esmolol (125, 250 or 500 μg/kg/min, after respective loading doses of 125, 250 and 500 μg/kg) in reducing and controlling intraoperative and postoperative hypertension occurring with repair of coarctation of the aorta in neonates through 6 years. No placebo control group was included in the study design.

Efficacy was measured at 5 minutes after esmolol start; in addition, pharmacokinetic sampling was taken up to 15 minutes after esmolol start. After the 15 minute pharmacokinetic period, investigators were allowed to maintain, titrate or discontinue the blinded esmolol, or switch to open-label esmolol.

One hundred eighteen patients were treated with esmolol, and 116 were included in an ITT efficacy analysis. The two primary efficacy endpoints were SBP reduction at 5 minutes after esmolol start and the need for rescue medications at 5 minutes.

The results showed a decrease in SBP in all 3 dose groups with no statistically significant difference between groups in either the change from baseline or percent change from baseline. There was also no statistically significant difference across groups in either the percentage of patients meeting rescue criterion or patients receiving rescue therapy. In fact, no statistically significant finding was seen with regard to primary or secondary efficacy endpoints in study 20,015-004.

Study 20,015-005 was an uncontrolled study of the pharmacokinetics of a 1000 μg/kg loading dose followed by a 15 minute infusion of 300 μg/kg/min. in children (2-12 yrs) and adolescents (12-16 yrs) with SVT in the cardiac catheterization laboratory. Twenty-seven patients were treated with esmolol, of which 26 were included in the efficacy analysis and 22 in the pharmacokinetic analysis. SVT was terminated within 10 minutes of esmolol start in 65% of treated patients; SVT termination occurred in a mean time of 2 minutes after esmolol start. However, no efficacy conclusion can be drawn in this uncontrolled study.

Safety results were reviewed individually and combined from both studies. Most of the safety finding appear consistent with current labeling or are known post-operative/post-procedure events.

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Shari Targum

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