

**Memorandum**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

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**SUBJECT:** One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data  
Esmolol Hydrochloride for Injection (Brevibloc<sup>®</sup>): NDA 19-386

**\*\*This document contains proprietary data from IMS Health and Premier which cannot be shared outside of FDA without clearance from IMS Health and Premier obtained through the Office of Drug Safety.\*\***

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**EXECUTIVE SUMMARY**

This consult examines drug utilization trends for esmolol hydrochloride (Brevibloc<sup>®</sup>) in the pediatric population (ages 0-16 years). Sales data were examined for the four-year period September 2000 - August 2004, with a primary focus on sales patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Brevibloc<sup>®</sup> on August 22, 2003. Inpatient drug utilization patterns were examined for the one-year period March 2003 - February 2004, with a primary focus on utilization patterns 6 months before and 6 months after the granting of pediatric exclusivity. Because nearly all (99%) of Brevibloc sales are to hospitals and clinics, outpatient drug utilization patterns are not addressed. Use of this product in hospitalized pediatric patients does not appear to have changed over the one-year period examined.

The injectable beta blocker market consists of esmolol and propranolol. Sales of esmolol increased a relative 12.9% during September 2000 – August 2004 while sales of injectable propranolol declined a relative 19% during the same period. There does not appear to have been a change in sales after the granting of exclusivity in August 2003 as 1.3 million units were sold in both the year pre-exclusivity (September 2002 – August 2003) and in the year post-exclusivity (September 2003 – August 2004). Non-

Federal hospitals are the largest class of purchasers of esmolol accounting for approximately 89% of esmolol units sold during September 2003 – August 2004.

Use of esmolol in a sample of 389 acute care hospitals is primarily in the adult population who accounted for 16,577 discharges associated with at least one claim for esmolol in the 6 months post exclusivity. Pediatric patients aged 0-16 years represented less than 1% (151 discharges) of esmolol associated discharges during this same time period. Among pediatric discharges only, patients aged 0-1 years accounted for 13.7% of discharges associated with esmolol use during the 6 months before exclusivity (March - August 2003) and 15.9% of discharges associated with esmolol use during the 6 months after exclusivity (September 2003 - February 2004), patients aged 2-11 years accounted for 25.5% of discharges associated with esmolol use and 23.8% of discharges associated with esmolol use while patients aged 12-16 years accounted for 60.9% and 60.3% respectively. The frequency of use within the pediatric population by age did not change over the study period.

In pediatric hospitals, younger pediatric patients accounted for a relatively greater proportion of pediatric discharges associated with esmolol use with patients aged 0-1 years accounting for 22 discharges (22.2%) during March - August 2003 and 20 discharges (22.0%) during September 2003 - February 2004. Patients aged 2-11 years accounted for 27 discharges (27.3%) during March - August 2003 and 30 discharges (33.0%) during September 2003 - February 2004. Discharges of patients age 12-16 years in which esmolol was billed, accounted for 50 discharges (50.5%) during March - August 2003 and 41 discharges (45.0%) during September 2003 - February 2004.

The top primary discharge diagnosis ICD-9 categories for patients age 0-16 years who were discharged from Premier acute care hospitals with a claim for esmolol are “Injury and Poisoning” (ICD-9 800-999), “Congenital Anomalies” (ICD-9 700-759) and “Diseases of the Digestive System” (ICD-9 520-579). The top diagnosis categories for patients age 17 years and older with a claim for esmolol were “Infectious and Parasitic Diseases” (ICD-9 001-139) (51.7%) and “Neoplasms” (ICD-9 140-239) (33.0%).

The most frequent primary diagnoses for esmolol associated discharges from Premier network acute care hospitals during March 2003 – February 2004 in pediatric patients were “Idiopathic Scoliosis” (ICD-9 737.30), “Acute Appendicitis without Peritonitis” (ICD-9 540.9) and coarctation of aorta (ICD-9 747.10). The most common diagnoses for adults were Salmonella Septicemia (ICD-9 003.1), Clostridium difficile intestinal infection (ICD-9 008.45), and intestinal infection due to other organism (ICD-9 008.8).

## **INTRODUCTION**

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the reporting of adverse events associated with the use of the drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Esmolol hydrochloride for injection (Brevibloc<sup>®</sup> NDA 19-386) was approved on December 31, 1986, for supraventricular tachycardia, intraoperative and postoperative tachycardia and hypertension, and noncompensatory sinus tachycardia. Esmolol should be used when rapid, short term control is desired in situations such as pre- and post-surgery, during intubation, induction of anesthesia, and during surgery. Esmolol is not intended for use in chronic settings or where transfer to another agent is anticipated.

There are no approved pediatric indications and no labeling for use in patients under the age of 16 years. Brevibloc<sup>®</sup> is supplied as a 2500 mg-250 ml premixed bag, a 2000 mg-100ml double strength premixed bag, 100 mg-10ml ready to use vials, and a 2500mg-10ml ampules.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Brevibloc<sup>®</sup> for Injection (NDA 19-386) on August 22, 2003. No changes to the product labeling have been made since this exclusivity was granted. This review describes sales trends and inpatient drug use patterns for esmolol in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

## **DATA SOURCES**

This review describes the sales and inpatient drug use patterns of esmolol in the pediatric population as compared to the adult population in the 6 months before and after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail below.

### ***IMS HEALTH, NATIONAL SALES PERSPECTIVES™***

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. IMS Health, National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, vials, and market share. These data are based on national projections.

For this analysis, the sales trend for esmolol was examined from September 2000 – August 2004, inclusive.

### ***PREMIER™***

Premier maintains a large hospital drug utilization and financial database which contains information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly one out of every seven inpatient discharges in the United States is represented in Premier's database. Data are available from January 2000 through the present, but have a lag time of approximately 6 months. Premier's primary mission is to assist health care institutions in improving clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, Premier developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, number of beds, population served, payors, and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.

For this analysis, the total number of projected discharges associated with esmolol within Premier hospitals was examined for the time period from March 2003 – February 2004, inclusive. First, data from an average of 389 acute care hospitals contributing data across this time period was examined; then use was examined in the subset of 37 pediatric hospitals specifically.

## RESULTS

### I. Sales and Market Share

Sales of esmolol were examined from September 2000 through August 2004. Sales of esmolol increased a relative 12.9% over the time of this analysis from 1.2 million units (vials and premixed bags) sold during September 2000 – August 2001 to 1.3 million units sold during September 2003 – August 2004 (Table 1). Sales of injectable propranolol declined a relative 19% during the same period with 448 thousand units sold during September – August 2001 and 363 thousand units sold during September 2003 – August 2004. There does not appear to have been a change in sales after the granting of exclusivity in August 2003 as 1.3 million units were sold in both the year pre-exclusivity (September 2002 – August 2003) and in the year post-exclusivity (September 2003 – August 2004). Non-federal hospitals are the largest purchasers of esmolol, representing 88.8% (1.2 million) units sold during the period from September 2003 – August 2004, followed by federal facilities (6.9% - 90,000 units) and clinics (3.2% - 41,200 units)<sup>1</sup>. Combined, these three channels represent 99% of esmolol sales.

**Table 1. Total Number of Bags and Vials of Injectable Beta-Blockers Sold in the US During Sept 1, 2001 - August 31, 2004 (thousands)**

	Sept 2000 - Aug 2001	Sept 2001 - Aug 2002	Sept 2002 - Aug 2003	Sept 2003 - Aug 2004	Percent Change Sept 2001 – Aug 2004
<b>Esmolol</b>	1,155.3	1,258.2	1,301.5	1,303.7	12.9%
<b>Propranolol</b>	447.9	674.2	461.1	362.6	-19.0%

IMS Health, IMS National Sales Perspectives™, Moving Annual Totals September 2000 - August 2004, Data Extracted November 200 (File: 0411esm3.dvr)

### II. Inpatient Use and Demographics

#### *Acute Care Hospitals*

Overall, use of esmolol in the acute care hospitals remained stable across the one year study period. Use of esmolol is primarily in the adult population with pediatric patients ages 0-16 years representing less than 1% of esmolol associated discharges from Premier network acute care hospitals during March 2003 – February 2004. In these 389 hospitals, pediatric patients aged 0-16 years accounted for 161 discharges associated with esmolol use during the pre-exclusivity period of March 2003 – August 2003 and 151 discharges associated with esmolol use during the 6 month post-exclusivity period of September 2003 – February 2004. Among pediatric patients only, children aged 0-1 years accounted for 22 discharges associated with esmolol use (13.7%) during March - August 2003 and 24 discharges associated with esmolol use (15.9%) during September 2003 - February 2004. Patients aged 2-11 years accounted for 41 discharges associated with esmolol use (25.5%) in the 6 months pre-exclusivity and 36 discharges associated with esmolol use (23.8%) in the 6 months post exclusivity while patients aged 12-16 years

<sup>1</sup> IMS Health National Sales Audit- Combined. Data extracted 11-2004 (File: 0411esm3.dvr)

accounted for 98 discharges associated with esmolol use (60.9%) during March - August 2003 and 91 discharges associated with esmolol use (60.3%) during September 2003 - February 2004.

*Pediatric Care Centers*

In the subset of 37 pediatric hospitals, younger pediatric patients accounted for a relatively greater proportion of pediatric esmolol claims with patients aged 0-1 years accounting for 22 discharges associated with a claim for esmolol (22.2%) during March - August 2003 and 20 discharges (22.0%) during September 2003 - February 2004 (Table 2). Patients aged 2-11 years accounted for 27 discharges associated with a claim for esmolol (27.3%) during March - August 2003 and 30 discharges (33.0%) during September 2003 - February 2004. Patients aged 12-16 years in which esmolol was billed accounted for 50 discharges associated with a claim for esmolol (50.5%) during March - August 2003 and 41 discharges associated with a claim for esmolol (45.0%) during September 2003 - February 2004.

<b>Table 2: Total Number of Discharges Associated with Esmolol by Age Groups in Premier Network Hospitals (Acute Care and Pediatric), March 2003 – February 2004 (Premier™)</b>					
	<b>March 2003 – August 2003</b>			<b>September 2003 - February 2004</b>	
<b>Acute Care Hospitals (n=389*)</b>					
Total	17,172			16,557	
Age 0-16	161	0.9%		151	0.9%
Age 0-1	22	13.7%		24	15.9%
Age 2-11	41	25.5%		36	23.8%
Age 12-16	98	60.9%		91	60.3%
Age 17+	17,011		99.1%	16,406 99.1%	
<b>Pediatric Hospitals (n=37)**</b>					
Total	99			91	
Age 0-1	22	22.2%		20	22.0%
Age 2-11	27	27.3%		30	33.0%
Age 12-16	50	50.5%		41	45.0%
Premier Informatics, data extracted 11-2004 (File: esmolol by Pri Dx 11.3.04.xls)					
*Average number of hospitals submitting data during study period.					
**Included within the 389 acute care hospitals listed above					

The ICD-9 3 digit diagnosis classification category was used to evaluate the general situations in which esmolol is most often used (Table 3). The top primary discharge diagnosis categories for patients age 0-16 years who were discharged from Premier acute care hospitals with a claim for esmolol are “Injury and Poisoning” (ICD-9 800-999) which accounted for 72 (23%) of esmolol associated discharges, “Congenital Anomalies” (ICD-9 700-759) with 55 esmolol associated discharges (17.6%) and Diseases of the Digestive System (ICD-9 520-579) with 53 discharges associated with a claim for esmolol (17.0%). The top diagnosis categories for patients aged 17 years and older were “Infectious and Parasitic Diseases” (ICD-9 001-139) which accounted for 17,921 esmolol associated discharges (51.7%) and “Neoplasms” (ICD-9 140-239) accounting for 11,039 discharges (33.0%).

**Table 3: Top Primary Discharge Diagnosis Categories for Discharges Associated with Esmolol Use in Premier Network Acute Care Hospitals March 2003 - February 2004 (Premier™)**

Age Band	ICD-9 Range	ICD-9 3 Digit Classification Category	Discharges	Percent
<b>Age 0-16</b>				
	800-999	Injury and Poisoning	72	23.1%
	740-759	Congenital Anomalies	55	17.6%
	520-579	Diseases of the Digestive System	53	17.0%
	710-739	Musculoskeletal System and Connective Tissue	47	15.1%
		Total Others (192)	85	27.2%
<b>Age 17 +</b>				
	001-139	Infectious and Parasitic Diseases	17,291	51.7%
	140-239	Neoplasms	11,039	33.0%
		Total Others (15)	5,087	15.2%

Premier Informatics Data extracted 11-04 (File: Esmolol by Pri Dx 11.03.04.xls)

We also examined the more specific 5 digit primary discharge diagnosis codes for discharges associated with esmolol use (Table 4). The most frequent primary discharge diagnoses for esmolol associated discharges from Premier network acute care hospitals during March 2003 – February 2004 in pediatric patients were “idiopathic scoliosis” (ICD-9 737.30) with 29 discharges, “acute appendicitis without peritonitis” (ICD-9 540.9) and “coarctation of aorta” (ICD-9 747.10) both accounting for 14 discharges each (Table 4). The most common discharge diagnoses for adults associated with esmolol use were “Salmonella septicemia” (ICD-9 003.1) with 3,971 discharges, “*Clostridium difficile* intestinal infection” (ICD-9 008.45) with 1,478 discharges, and “intestinal infection due to other organism” (ICD-9 008.8) with 1,000 discharges

**Table 4: Top Primary Discharge Diagnosis for Discharges in Which Patients Were Billed for Esmolol in Premier Network Acute Care Hospitals March 2003 - February 2004 (Premier™)**

Age Band	ICD-9	Diagnosis	Discharges
<b>Age 0-16</b>			
	737.30	Scoliosis, Idiopathic	29
	540.9	Acute Appendicitis w/o Peritonitis	14
	747.10	Coarctation of Aorta	14
		Total Others (192)	255
<b>Age 17 +</b>			
	003.1	Salmonella Septicemia	3,971
	008.45	Intestinal Infection - <i>Clostridium difficile</i>	1,478
	008.8	Intestinal Infection Due Other Organism	1,000
		Total Others (2174)	27,148

Premier Informatics Data extracted 11-04 (File: Esmolol by Pri Dx 11.03.04.xls)

## DISCUSSION

The IMS Health, National Sales Perspectives™ does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients receiving these products, such as age and gender. The amount of products purchased by these retail and non-retail channels of distribution may be a possible

surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use. Due to the typical situations in which esmolol may be used, we expect that some of the product may be stocked in emergency carts (crash carts) and may become outdated and discarded before being administered to a patient.

National projections are not possible with age stratified Premier data. In addition, since the time course of events that occur during a hospitalization is not recorded in the Premier database, it is not possible to directly link the drugs used to specific diagnoses/procedures. Therefore, the data provided reflect the use of esmolol only within a sample of acute care hospitals, and a subset of children's hospitals.

## CONCLUSIONS

The injectable beta blocker market consists of esmolol and propranolol. Sales of esmolol increased a relative 12.9% from 1.2 million units sold during September 2000 – August 2001 to 1.3 million units sold during September 2003 – August 2004. Over the same time period, sales of injectable propranolol declined a relative 19% with 448 thousand units sold to 363 thousand units sold. There does not appear to have been a change in sales after the granting of exclusivity in August 2003 as 1.3 million units were sold in both the year pre-exclusivity (September 2002 – August 2003) and in the year post-exclusivity (September 2003 – August 2004). Non-Federal hospitals purchased 88.8% of esmolol sold during September 2003 – August 2004.

Use of esmolol in a sample of 389 of acute care hospitals was primarily in the adult population who accounted for 16,557 discharges associated with a claim for esmolol in the 6 months post exclusivity. Pediatric patients aged 0-16 years represented less than 1% (151 discharges) of esmolol associated discharges during this time period. The frequency of use within the pediatric population by age did not change over the study period.

In the subset of pediatric hospitals, younger pediatric patients accounted for a relatively greater proportion of pediatric discharges associated with esmolol use with patients aged 0-1 years accounting for 22 discharges (22.2%) during March - August 2003 and 20 discharges (22.0%) during September 2003 - February 2004 (Table 2). Patients aged 2-11 years accounted for 27 discharges (27.3%) during March - August 2003 and 30 discharges (33.0%) during September 2003 - February 2004. Patients aged 12-16 years in which esmolol was billed accounted for 50 discharges (50.5%) during March - August 2003 and 41 discharges (45.0%) during September 2003 - February 2004.

The top primary discharge diagnosis ICD-9 categories for patients age 0-16 years who were discharged from Premier acute care hospitals with a claim for esmolol are “Injury and Poisoning” (ICD-9 800-999), “Congenital Anomalies” (ICD-9 700-759) and “Diseases of the Digestive System” (ICD-9 520-579). The top discharge diagnosis categories for patients age 17 years and older with a claim for esmolol were “Infectious and Parasitic Diseases” (ICD-9 001-139) (51.7%) and “Neoplasms” (ICD-9 140-239).

The most frequent primary diagnoses for esmolol associated discharges from Premier network acute care hospitals during March 2003 – February 2004 in pediatric patients were “Idiopathic Scoliosis” (ICD-9 737.30), “Acute Appendicitis without Peritonitis” (ICD-9 540.9) and coarctation of aorta (ICD-9 747.10). The most common discharge diagnoses associated with esmolol use for adults were Salmonella Septicemia (ICD-9 003.1), Clostridium difficile intestinal infection (ICD-9 008.45), and intestinal infection due to other organism (ICD-9 008.8).