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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

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Subject: Pediatric Drug Use Update

Drug Name(s): Brevibloc[®] (esmolol)

Application Type/Number: NDA 19-386

Submission Number:

Applicant/sponsor: Baxter Healthcare Corporation

OSE RCM #: 2007-2130

EXECUTIVE SUMMARY

This review is an update to the utilization review that was conducted on December 14, 2004, examining the drug utilization patterns for Esmolol, a beta adrenergic antagonist, in the pediatric population, patients aged 0-16 years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on August 22, 2003. Since approximately 99% of bag/vials of esmolol were sold in U.S. non-retail channels of distribution during the pre- and post- exclusivity periods, we focused on utilization patterns in the inpatient setting. An inpatient proprietary drug use database licensed by FDA was used to examine the patterns of use for Esmolol during the three 12-month periods from September 2004 through August 2007.

The use of esmolol in acute care hospitals has increased approximately 20% from approximately 35,710 discharges to 42,674 discharges over the three 12-month study periods from September 2004 – August 2007. Inpatient discharges with a billing charge for esmolol within the pediatric population accounted for approximately 1% (average 406 discharges) of the total inpatient unprojected discharge data. The principal diagnoses associated with esmolol for pediatric patients were “idiopathic scoliosis” (ICD-9 737.30), “coarctation of aorta, preductal” (ICD-9 747.10), and “acute appendicitis without peritonitis” (ICD-9 540.9).

1 INTRODUCTION

On January 4, 2002, 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 review of adverse events associated with the use of a 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 Committee on the drug utilization patterns and adverse events associated with the use of the drug soon after the one-year anniversary of granting exclusivity. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

1.1 REGULATORY HISTORY

Esmolol hydrochloride for injection (Brevibloc[®], 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[®] 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[®] 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.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for esmolol. The examination of wholesale sales data for September 2004 – August 2007 indicates that approximately 99% of esmolol bags/vials were distributed to non-retail settings (approximately 86% non-federal hospitals; 7% to federal facilities);¹ thus, we examined inpatient utilization patterns.

2.2 DATA SOURCES

We used data from Premier Healthcare Informatics, RxMarket Advisor™ to examine inpatient utilization patterns for unprojected discharges and principal diagnostic ICD-9 codes associated with a billing charge for esmolol, stratified by ages 0-1 year, 2-11 years, and 12-16 years for the three 12-month study periods from September 1, 2004 – August 31, 2007. Complete descriptions of the databases used can be found in the Appendix.

3 RESULTS

Overall, the use of esmolol in acute care hospitals has increased approximately 20% from approximately 35,710 discharges during September 1, 2004 – August 31, 2005 to 42,674 discharges during September 1, 2006 – August 31 2007 (Table 1). Inpatient discharges with a billing charge for esmolol within the pediatric population accounted for approximately 1% (average 406 discharges) of the total inpatient unprojected discharge data (Table 1). Among pediatric patients, children aged 12-16 accounted for the majority of pediatric esmolol claims.

¹ IMS Health, IMS National Sales Perspectives™, September 2006 – August 2007, Extracted October 2007. Original File: 0710esmo.dvr.

Table 1: Total Unprojected Discharges Associated with Esmolol by Age Groups in Premier Network Hospitals from September 2004 - August 2007

	September 2004 - August 2005		September 2005 - August 2006		September 2006 - August 2007		Total	
	Unprojected Discharges	Share (%)	Unprojected Discharges	Share (%)	Unprojected Discharges	Share (%)	Unprojected Discharges	Share (%)
Acute Care Hospitals (n=493)								
Total	35,710	100.0%	41,337	100.0%	42,674	100.0%	119,721	100.0%
Pat Age 0-16	362	1.0%	411	1.0%	444	1.0%	1,217	1.0%
Pat Age 0-1	88	24.3%	86	20.9%	119	26.8%	293	24.1%
Pat Age 2-11	66	18.2%	96	23.4%	87	19.6%	249	20.5%
Pat Age 12-16	208	57.5%	229	55.7%	238	53.6%	675	55.5%
Age 17+	35,348	99.0%	40,926	99.0%	42,230	99.0%	118,504	99.0%
Subset of Pediatric Hospitals (n=41)								
Total (Pat Age 0-16)	357	100.0%	406	100.0%	438	100.0%	1,201	100.0%
Pat Age 0-1	88	24.6%	86	21.2%	119	27.2%	293	24.4%
Pat Age 2-11	61	17.1%	91	22.4%	81	18.5%	233	19.4%
Pat Age 12-16	208	58.3%	229	56.4%	238	54.3%	675	56.2%

Premier RxMarket Advisor™, Data extracted 1-2008.

Source File: PREMIER 2007-2130 Esmolol 12-13-07.xls

The most frequent principal discharge diagnoses associated with esmolol use were also examined (Table 2). The most frequent principal discharge diagnoses during the entire study period in the pediatric population associated with esmolol in Premier's network of acute care hospitals were "idiopathic scoliosis" (ICD-9 737.30) with a total of 90 discharges, "coarctation of aorta, preductal" (ICD-9 747.10) with 80 discharges, and "acute appendicitis without peritonitis" (ICD-9 540.9) with 54 discharges. The most common principal diagnosis associated with esmolol for adults were "coronary atherosclerosis" (ICD-9 414.01), "carotid artery occlusion and stenosis" (ICD-9 433.10), and "acute MI subendocardial infarct" (ICD-9 410.71).

Table 2: Top Principal Diagnosis for Discharges in which patients were billed for Esmolol in Premier Network Acute Care Hospitals March 2004 - August 2007

Principal Dx ICD9	September 2004- August 2005		September 2005- August 2006		September 2006- August 2007		Total	
	Unprojected Discharges	Share (%)	Unprojected Discharges	Share (%)	Unprojected Discharges	Share (%)	Unprojected Discharges	Share (%)
TOTAL, Age 0-16	362	100.0%	410	100.0%	444	100.0%	1,216	100.0%
737.30 Scoliosis, Idiopathic	21	5.8%	28	6.8%	41	9.2%	90	7.4%
747.10 Coarctation of aorta, preductal	25	6.9%	24	5.9%	31	7.0%	80	6.6%
540.9 Acute Appendicitis w/o Peritonitis	16	4.4%	19	4.6%	19	4.3%	54	4.4%
Total Others (493)	300	82.9%	339	82.7%	353	79.5%	992	81.6%
TOTAL, Age 17 and older	35,344	100.0%	40,890	100.0%	42,183	100.0%	118,417	100.0%
414.01 Coronary Atherosclerosis	3,497	9.9%	3,514	8.6%	3,296	7.8%	10,307	8.7%
433.10 Carotid Artery Occlusion & Stenosis	1,576	4.5%	1,582	3.9%	1,814	4.3%	4,972	4.2%
410.71 Acute MI Subendocardial Infarct	959	2.7%	904	2.2%	968	2.3%	2,831	2.4%
Total Others (3475)	29,312	82.9%	34,890	85.3%	36,105	85.6%	100,307	84.7%

Premier RxMarket Advisor™, Data extracted 1-2008.

Source File: PREMIER 2007-2130 Esmolol Diag 12-14-07.xls

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We conducted a comprehensive analysis of the use of this product in the inpatient setting; however, these data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use if it is assumed that facilities purchase drugs in quantities reflective of actual patient use.

Inpatient data also have limitations to consider when interpreting use estimates. Premier data are derived from hospital billing data, and therefore may not reflect exactly what drugs are administered to patients. Also, there are no direct linkages between billed drugs and discharge diagnoses and procedures, so indications for use cannot be determined. Finally, we are currently not able to use Premier data to make reliable national estimates of drug use for the subpopulation of pediatric inpatients. Although Premier hospitals appear representative of all U.S. acute short-stay hospitals in general, it is not clear whether they are representative of pediatric inpatient care in the U.S.

5 CONCLUSIONS

Similar to the previous BPCA drug utilization review completed on December 14, 2004, approximately 1% of esmolol-associated discharges from September 2004 – August 2007 were for pediatric patients aged 0-16 years.² The principal diagnoses for pediatric patients have also remained similar: “idiopathic scoliosis” (ICD-9 737.30), “coarctation of aorta, preductal” (ICD-9 747.10), and “acute appendicitis without peritonitis” (ICD-9 540.9). Overall, the use of esmolol in acute care hospitals has increased approximately 20% from approximately 35,710 discharges to 42,674 discharges over the three 12-month study periods from September 2004 – August 2007.

CONCURRENCE

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² Money, D. Esmolol BPCA Drug Utilization Review 12-14-04

APPENDIX

APPENDIX 1: Database Descriptions

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS 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. Volume is expressed in terms of sales dollars, eases, extended units, and share of market. These data are based on national projections. 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.

Premier RxMarket Advisor

Premier's database is a large hospital drug utilization and financial database. Information is available from over 590 acute care and pediatric facilities and includes approximately 38 million inpatient records. On an annual basis, this constitutes roughly one out of every six inpatient discharges in the United States. Data are available from January 2000 through the present, but have a lag time of approximately 75 days. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, the Premier Informatics group 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, bed size, 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. Based upon these analyses, FDA believes that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommends making this determination on a drug-specific basis.

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/s/

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