

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 20, 2004

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SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event  
Review, PID#D030528  
Drug: Esmolol, NDA#19-386  
Pediatric Exclusivity Approval Date: August 22, 2003

**Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.**

**Executive Summary**

The AERS database was searched for reports of adverse events occurring with the use of esmolol in pediatric patients. Overall, AERS contains 276 reports (raw count) for esmolol. Pediatric reports represented 13 (raw count) of the total number of reports. Only 1 of the 7 (raw count) reports obtained during the pediatric exclusivity period, August 22, 2003 to September 22, 2004, involved a pediatric patient. This case did not report a fatal outcome.

We reviewed one pediatric case reported to the FDA during the pediatric exclusivity period. This report described a case of a sixteen year old who was administered multiple drugs during surgery and experienced an acute hypertensive crisis, sinus tachycardia, myocardial ischemia, myocardial depression, and pulmonary oedema<sup>1</sup>. It is likely that esmolol contributed to the depression of myocardial contractility. This is a labeled event for this drug. This review did not highlight any significant safety concerns regarding esmolol use in children.

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<sup>1</sup> Kademani D, Voiner JL, Quinn PD. Acute hypertensive crisis resulting in pulmonary edema and myocardial ischemia during orthognathic surgery. Journal of Oral and Maxillofacial Surgery. 2004; 62(2): 240-3

**AERS Search Results: Esmolol**

AERS search includes all sources- U.S. & Foreign

**A. From marketing approval date (December 31, 1986) through AERS data cut-off date (September 22, 2004).**

1. Counts of Reports: Table 1 (parentheses denote U.S. origin report counts)

<b>Table 1: Raw counts of reports from marketing approval date through AERS data cut-off date</b>			
	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	276 (230)	158 (136)	63 (59)
Adults (≥17)	159 (142)	110 (96)	48 (45)
Peds (0-16)	13 (13)	9 (9)	3 (3)

Reporting trends for pediatric reports from approval date (December 31, 1986): see Table 2

<b>Table 2: Reporting trend for pediatric reports from approval date (December 31,1986)</b>	
Year	Number of reports
1991	2
1992	3
1995	1
1998	4
1999	1
2000	1
2004	1

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups since drug approval: see Table 3 (Events not previously described in the product label<sup>2</sup> are underlined; bolded events are unique to top 20 events in pediatric patients relative to adults)

<b>Table 3: Counts of top 20 reported event preferred terms (from approval date)</b>		
All ages (includes null ages)	Cardiac Arrest <sup>3</sup> -56	Injection Site Necrosis-11
	Hypotension-49	<u>Drug Ineffective-10</u>
	Bradycardia-43	<u>Apnoea-9</u>
	<u>Medication Error-40</u>	<u>Myocardial Infarction-9</u>
	<u>Accidental Overdose-37</u>	Atrioventricular Block <sup>4</sup> -7
	Injection Site Reaction-22	Coma <sup>5</sup> -7
	<u>Myocardial Ischaemia-20</u>	<u>Hypertension-7</u>
	<u>Tachycardia-16</u>	Pulmonary Oedema-7
	<u>Overdose-12</u>	<u>Acidosis-6</u>
	Convulsion-11	Asthma <sup>6</sup> -6

<sup>2</sup> Labeling information obtained from esmolol/Brevibloc® label (Baxter International Inc.) Revised June 2003

<sup>3</sup> Labeled as occurring during esmolol overdose or if used in conjunction with verapamil in patients with depressed myocardial function

Table 3: Counts of top 20 reported event preferred terms (from approval date)		
Adults (17+ years)	Cardiac Arrest <sup>3</sup> -42 Hypotension-34 Bradycardia-29 <u>Accidental Overdose-27</u> <u>Medication Error-24</u> Injection Site Reaction-16 <u>Tachycardia-9</u> <u>Apnoea-8</u> <u>Overdose-8</u> Atrioventricular Block <sup>4</sup> -6	Convulsion-6 Pulmonary Oedema-6 Agitation-5 Coma <sup>5</sup> -5 <u>Condition Aggravated-5</u> <u>Hypertension-5</u> Injection Site Necrosis-5 <u>Myocardial Infarction-5</u> Skin Necrosis <sup>7</sup> -5 <u>Blister-4</u>
Pediatric patients (0-16 years)	Cardiac Arrest <sup>3</sup> -3 Blood Pressure Decreased-2 Convulsion-2 Hypotension-2 <u>Urticaria-2</u> <u>Amnesia-1</u> <u>Body Temperature decreased-1</u> <u>Cardiac Disorder-1</u> Coma <sup>5</sup> -1 Drug Interaction-1	<u>Drug Level Above Therapeutic-1</u> <u>Electrocardiogram ST Segment Elevation-1</u> <u>Extravasation-1</u> Grand Mal Convulsion <sup>8</sup> -1 Heart Rate Decreased-1 <u>Hypertensive crisis-1</u> <u>Hyponatraemia-1</u> <u>Hypoventilation-1</u> <u>Inflammation-1</u> <u>Injection Site Erythema-1</u>

**B. From Pediatric Exclusivity approval date (August 22, 2003) through AERS data cut-off date (September 22, 2004):**

1. Counts of reports: Table 4

Table 4: Raw counts of reports from pediatric exclusivity approval date through AERS data cut-off date			
	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	7 (6)	7 (6)	3 (3)
Adults (≥17)	4 (3)	4 (3)	2 (2)
Peds (0-16)	1 (1)	1 (1)	0

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups: see Table 5 (Events not previously described in the product label<sup>2</sup> are underlined; bolded events are unique to events in pediatric patients relative to top 20 events in adults)

<sup>4</sup> Labeled as heart block

<sup>5</sup> Labeled as loss of consciousness during overdose

<sup>6</sup> Labeled as bronchospastic disease

<sup>7</sup> Labeled as local skin necrosis from extravasation

<sup>8</sup> Labeled as convulsion

<b>Table 5: Counts of top 20 reported event preferred terms (from pediatric exclusivity date)</b>		
All ages	<u>Alcohol Withdrawal Syndrome</u> -2 <u>Aspiration</u> -2 Bradycardia-2 Electromechanical Dissociation <sup>9</sup> -2 Hypotension-2 <u>Myocardial Infarction</u> -2 <u>Respiratory Acidosis</u> -2 <u>Respiratory Failure</u> -2 <u>Ventricular Fibrillation</u> -2 <u>Ventricular Tachycardia</u> -2	Agitation-1 Atrioventricular Block <sup>4</sup> -1 <u>Body Temperature Decreased</u> -1 Cardiac Arrest <sup>3</sup> -1 Cardiac Failure-1 <u>Cardiac Procedure Complication</u> -1 Cardio-Respiratory Arrest <sup>3</sup> -1 Confusional State-1 Disorientation <sup>10</sup> -1 <u>Drug Effect Decreased</u> -1
Adults (17+ years)	<u>Alcohol Withdrawal Syndrome</u> -2 <u>Aspiration</u> -2 Bradycardia-2 Electromechanical Dissociation <sup>9</sup> -2 Hypotension-2 <u>Myocardial Infarction</u> -2 <u>Respiratory Acidosis</u> -2 <u>Respiratory Failure</u> -2 <u>Ventricular Fibrillation</u> -2 <u>Ventricular Tachycardia</u> -2	Agitation-1 Atrioventricular Block <sup>4</sup> -1 Cardiac Arrest <sup>3</sup> -1 Cardiac Failure-1 <u>Cardiac Procedure Complication</u> -1 Confusional State-1 Disorientation <sup>10</sup> -1 <u>Drug Effect Decreased</u> -1 <u>General Physical Health Deterioration</u> -1 <u>Graft Complication</u> -1
Pediatric patients (Total PTs=7)	<b><u>Body Temperature Decreased</u>-1</b> <b><u>Electrocardiogram ST Segment Elevation</u>-1</b> <b><u>Hypertensive crisis</u>-1</b> <b><u>Myocardial Ischaemia</u>-1</b> <b><u>Pulmonary Oedema</u>-1</b> <b><u>Respiratory Rate Decreased</u>-1</b> <b><u>Sinus Tachycardia</u>-1</b>	

**Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after pediatric market exclusivity was granted**

**A. Demographic characteristics of pediatric report regarding gender, age, indication, dose, and outcome:**

<b>Table 6: Characteristics of the pediatric case received during the 1-year period after receiving pediatric market exclusivity (N=1)</b>	
Gender	Female
Age	16 years
Indication for which the drug was used	Acute hypertensive crisis and sinus tachycardia
Dose	90mg
Outcome	Life Threatening

<sup>9</sup> Labeled as occurring during overdose

<sup>10</sup> Labeled as confusion

**B. Comments regarding labeling status of the top 20 adverse events and similarities to adult adverse event profile.**

Only one pediatric case was reported during this period, therefore no PT count is greater than one. Out of the 7 PTs obtained for this report, one PT is labeled in the adult population (pulmonary oedema) and the six remaining PTs are unlabeled (see Section C). None of the 7 PTs appear as top 20 PTs for the adult population during the period from marketing to the end of the Pediatric Exclusivity. This is not unusual as there is only one pediatric case from which the seven PTs have been obtained.

**C. Comments and analysis of events not recognized for adult population.**

One pediatric report was received during the requested period after pediatric exclusivity was granted. This report described a case of a sixteen year old who was administered multiple drugs during surgery and experienced an acute hypertensive crisis, sinus tachycardia, pulmonary oedema and myocardial ischemia<sup>1</sup>. Out of a total of 7 PTs obtained from this report, 6 are unrecognized (unlabeled) in the adult population (See Table 5). Of these 6 PTs, 2 PTs (hypertensive crisis and sinus tachycardia) are related to the condition of the patient prior to esmolol administration, and the remaining four PTs are related to an episode of myocardial ischemia (electrocardiogram ST segment elevation, myocardial ischemia, pulmonary oedema and respiratory rate decreased), which is discussed in more detail in Section F.

**D. Comments and analysis of events uniquely identified in children but not reported in adult population, including increased frequency of any expected events. Recommended actions, if appropriate, after consultation with HFD-960 and OND Review Division (HFD-110).**

It is not possible to make a valid comment regarding increased frequency of reporting from only one pediatric report for esmolol.

**E. Summary and comment on death reports.**

There were no reports of death occurring in pediatric patients for esmolol.

**F. Summary of pediatric adverse event profile during period.**

ISR#4433065; 2004; United States:

This case, which was published in the literature, reported a 16 year old female who was taken into the operating room for an osteotomy in preparation for mandible surgery<sup>1</sup>. The patient had no relevant medical history, was not taking any regular medications, and had no known drug allergies. The patient's pre-operative vital signs were normal except for a low temperature (35.4 degrees centigrade). The patient was treated with diazepam

intravenous (IV) (2mg), topical phenylephrine (0.5%, one spray in each nostril), glycopyrrolate IV (0.5mg), cefazolin IV (1g), dexamethasone IV (10mg), propofol IV (120mg), lidocaine IV (80mg), fentanyl (100 mcg IV) and vecuronium (5mg IV). Balanced general anesthesia was maintained with isoflurane, nitrous oxide and oxygen. One percent lidocaine with 1: 100000 epinephrine was administered to the surgical site as a local anesthetic. Ten minutes into the operation the patient became acutely hypertensive with a persistent blood pressure of 200/100mmHg and sinus tachycardia at a rate of 150 beats per minute. At this time esmolol IV (90mg) was given in an attempt to control her blood pressure. Approximately ten minutes later, with half of the osteotomy complete, a pink frothy exudate was noticed in the endotracheal tube. The patient's oxygen requirements increased and 100% oxygen was administered to keep her oxygen saturation above 95%. The procedure was halted and the endotracheal tube was aggressively suctioned. A chest x-ray revealed fulminant pulmonary oedema. An electrocardiogram showed global elevation in all ST segments and sinus tachycardia. The patient continued to require endotracheal suctioning, while attempts were made to normalize her blood pressure. Gradually, her hemodynamic instability resolved and her blood pressure and pulse rates normalized (BP 110 to 135/70 mmHg, pulse 90 to 110 bpm). Postoperative ECGs indicated T-wave abnormality and a prolonged QT. Cardiac enzymes, one hour post-op, revealed a troponin level of 3.5 (normal value <0.3), indicating myocardial ischemia. With continued medical management her condition gradually improved and she recovered.

### **Summary**

The AERS database was searched for reports of adverse events occurring with the use of esmolol in pediatric patients. We focused on the 1-year period following the FDA approval of pediatric exclusivity for esmolol, August 22, 2003 to September 22, 2004. Only 1 of the 7 (raw count) reports obtained during the pediatric exclusivity period involved a pediatric patient. This pediatric case did not report a fatal outcome. The adverse event preferred terms obtained for the pediatric report during this period was compared to those obtained for adults for the same period.

We reviewed the pediatric case reported to the FDA during the Pediatric Exclusivity period. This case described the use of esmolol in a patient who was experiencing an acute hypertensive crisis and sinus tachycardia during an osteotomy operation<sup>1</sup>. Following esmolol administration the patient developed pulmonary oedema and it was determined that myocardial ischemia had occurred at some time during the operation. It is most likely that a combination of epinephrine, phenylephrine, glycopyrrolate, isoflurane and nitrous oxide was responsible for the acute hypertensive crisis, sinus tachycardia, and subsequent myocardial ischemia and depressed myocardial contractility. It is likely that esmolol contributed to the depressed myocardial contractility and this is a known (labeled) event.

From the available information we do not consider that there are any additional safety concerns at this time regarding the use of esmolol in the pediatric population. We will continue to monitor for adverse event reports in this patient group.

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Concur:

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Susan Lu  
Team Leader

## Appendix

### Standard Searches:

- A. Adults (17 yrs and above)
  - 1. All outcomes from AP date (no set criteria)
  - 2. Serious outcomes from AP date
  - 3. Death as an outcome from AP date
  - 4. All outcomes from PE date to present or any desired date
  - 5. Serious outcomes from PE date to present or any desired date
  - 6. Death as an outcome from PE date to present or any desired date
  
- B. Ages 0-16 yrs ONLY
  - 1. Same as above 1-6
  - 2. Retrieve case reports for hands-on review

### Standard Printouts for Attachments:

- A. Adults (17 yrs and above)
  - 1. Frequency counts of all preferred terms (PT) in cases
  - 2. Frequency counts of all PT in cases with serious outcomes
  - 3. Frequency counts of all PT in cases with death as an outcome
  - 4. Frequency counts of cases by Gender and ages
  
- B. Ages 0-16 yrs ONLY
  - Same as above 1-4

## Drug Product Information

### Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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