

One Year Post Exclusivity Adverse Event Review: Esmolol

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Background Drug Information

- **Drug:** Brevibloc[®] (esmolol HCL)
- **Therapeutic Category:** beta-1-selective (cardioselective) adrenergic receptor blocking agent
- **Sponsor:** Baxter Laboratories
- **Adult Indication:** Treatment of supraventricular tachycardia (SVT); intra-operative and post-operative tachycardia and/or hypertension
- **No Pediatric Indication**
- **Original Market Approval:** December 31, 1986
- **Pediatric Exclusivity Granted:** August 22, 2003

Drug Use Trends: Esmolol

- No change in total annual sales of 1.3 million units of esmolol between one year pre-exclusivity (9/02 - 8/03) and one year post-exclusivity (9/03-8/04)¹
- 99% of total sales to inpatient facilities¹
- Almost all of the inpatient use is in adults.²
- Pediatric use < 1% of all in-patient use²
 - 161 of 17,172 (0.9%) discharges associated with esmolol during pre-exclusivity period of Mar 2003 - Aug 2003²
 - 151 of 16,557 (0.9%) discharges in 6 month post-exclusivity period of Sep 2003 - Feb 2004²

¹IMS Health, IMS National Sales Perspectives™, Moving Annual Totals, Sep 2000 - Aug 2004, Data Extracted Nov 2004

²Premier Informatics, Mar 2003 – Feb 2004, Data Extracted Nov 2004

Pediatric Exclusivity Studies: PK/PD

- 27 patients with SVT, 2-16 years of age
- Dosing of esmolol: 1000 ug/kg loading, followed by 15 minute infusion of 300 ug/kg/minute
- SVT terminated within 10 minutes in 65% of treated patients; mean termination time 2 minutes

Pediatric Exclusivity Studies: Efficacy

- Randomized, double blind comparison of efficacy of three different doses (125, 250, 500 ug/kg) of drug in controlling intra- and post-operative hypertension with repair of coarctation of aorta
- 118 patients, neonates through 6 years of age
- Efficacy endpoints:
 - systolic blood pressure (SBP) reduction at 5 minutes
 - need for rescue medications at 5 minutes

Pediatric Exclusivity Studies: Efficacy Results

- SBP decreased in all dose groups with no significant difference among groups in change from baseline
- No significant difference across groups in percentage of patients meeting rescue criteria or receiving rescue therapy

Pediatric Exclusivity Studies: Safety

- 145 patients in two studies evaluated
- 7 withdrawals due to adverse events (AEs):
Hypotension (5), injection site reaction (1),
wheezing (1)
- No deaths or other serious AEs
- 134 (92%) patients with one or more AEs
 - AEs consistent with adult labeling

Relevant Safety Labeling

- Safety results were reviewed individually and combined from both pediatric studies. Most of the safety findings appear consistent with current labeling or are known post-operative/post-procedure events.
- No new safety labeling resulted from the pediatric studies.

Adverse Event Reports since Market Approval: Esmolol 12/31/86 - 9/22/04

- Total number of reports, all ages^{†*}:
 - 276 reports (230 US)
 - 158 serious (136 US)
 - 63 deaths (59 US)
- Pediatric reports^{*}:
 - 13 reports (13 US)
 - 9 serious (9 US)
 - 3 deaths (3 US)

[†]Includes reports with unknown age

^{*}Counts may include duplicate reports

Pediatric Deaths since Market Approval (n=3)

- 2 ½ month female with major heart defect; surgical repair of coarctation of aorta followed by dilation of aorta 2 weeks later
- Unspecified surgery 4 days later, during which SVT occurred and esmolol given. BP “bottomed out” 12 hours post-operatively, patient had “inflammatory response” and expired. Concomitant medications were dopamine and fentanyl.
- Autopsy: Necrotic tissue in patient's heart and lungs

Pediatric Deaths since Market Approval (n=3)

- 16 y.o. female; overdose of theophylline in suicide attempt (serum level 180 mcg/ml)
- Tachycardia (HR>100) ensued and IV esmolol 600 mcg/kg infused during one minute followed by infusion of 60 mcg/kg/minute
- Grand mal convulsion occurred after three minutes and esmolol was stopped.
- Apnea, cardiac arrest, resuscitation medications given
- Irreversible coma, death

Pediatric Deaths since Market Approval (n=3)

- 5 y.o. male; surgery for hypoplastic aortic arch; received nitroprusside for post-operative hypertension
- Esmolol added
- Increased levels of cyanide and thiocyanate; nitroprusside stopped and levels decreased
- Reactions described as “drug interaction” and “drug level above therapeutic”
- Death 5 days after surgery due to “surgical failure”

Most Common Adverse Events since Market Approval

- Most common AEs (2-3 occurrences) for **pediatric** patients: cardiac arrest, hypotension, blood pressure decreased, convulsion, and urticaria
- Most common AEs (5 or more occurrences) for **adult** patients: cardiac arrest, hypotension, bradycardia, accidental overdose, medication error, injection site reaction, tachycardia, apnea, overdose, AV block, convulsion, pulmonary edema, agitation, coma, condition aggravated, hypertension, injection site necrosis, skin necrosis, myocardial infarction

Underlined events = Unlabeled events

Adverse Event Reports during the One-Year Post-Exclusivity Period: Esmolol 08/22/03 - 09/22/04

- Total number of reports, all ages^{†*}:
 - 7 reports (6 US)
 - 7 serious (6 US)
 - 3 deaths (3 US)
- Pediatric reports^{*}:
 - 1 report (1 US)
 - 1 serious (1 US)
 - No deaths

[†]Includes reports with unknown age

^{*}Counts may include duplicate reports

Pediatric Adverse Events during the One-Year Post-Exclusivity Period (n=1)

- A teenage female patient undergoing osteotomy for correction of retrognathia received multiple medications during surgery.
- Normal pre-operative vital signs except for low temperature (35.4 °C)
- After 10 minutes of surgery, acute hypertensive crisis (200/100 mm Hg) and sinus tachycardia (150/minute) occurred for which IV **esmolol** was given.
- Chest x-ray: pulmonary edema
- ECG: global ST segment elevation
- Elevated Troponin level of 3.5 ng/ml (normal < 0.3) obtained one hour post-operatively, indicative of myocardial ischemia
- Surgery halted, patient stabilized and recovered

Summary: Esmolol

- No pattern discernible in pediatric AEs
- This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.
- FDA recommends routine monitoring of AEs for this drug in all populations.
- Does the Advisory Committee concur?

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