

**Pediatric Focused Safety Review
Bloxiverz™ (neostigmine methylsulfate)
Pediatric Advisory Committee Meeting
September 14, 2016**

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Center for Drug Evaluation and Research
Food and Drug Administration**

Outline

- **Background Information**
- Clinical Studies
- Drug Use Trends
- Safety
- Summary

Background Drug Information

Bloxiverz™ (neostigmine methylsulfate)

- **Drug:** Bloxiverz™ (neostigmine methylsulfate)
- **Formulation:** injection for intravenous use
- **Sponsor:** Éclat Pharmaceuticals
- **Original Market Approval:** May 31, 2013
- **Therapeutic Category:** Cholinesterase inhibitor

Neostigmine has been marketed as an unapproved product since 1939.

Background Drug Information, continued

Bloxiverz™ (neostigmine methylsulfate)

Indication (all ages): For the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery

Background Drug Information, continued

Bloxiverz™ (neostigmine methylsulfate)

4 Contraindications

- Known hypersensitivity to neostigmine
- Peritonitis or mechanical obstruction of the intestinal or urinary tract

5 Warnings and Precautions

- **Bradycardia** – atropine sulfate or glycopyrrolate should be administered prior to Bloxiverz™ to lessen the risk of bradycardia
- **Adverse reactions in patients with certain coexisting conditions** – Bloxiverz™ should be used with caution in patients with coronary artery disease, cardiac arrhythmias, recent coronary syndrome or myasthenia gravis
- **Hypersensitivity**
- **Neuromuscular dysfunction**
- **Cholinergic crisis**

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Clinical Studies

Bloxiverz™ (neostigmine methylsulfate)

- The evidence for the efficacy is derived from the published literature of studies conducted in the U.S. and outside of the U.S.
- Studies include randomized, spontaneous-recovery or placebo-controlled studies using similar efficacy endpoints
- A total of 404 adult and 80 pediatric patients undergoing various surgical procedures were evaluated
- Patients had reductions in their recovery time from neuromuscular blockade with neostigmine methylsulfate treatment compared to spontaneous recovery

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Pediatric Utilization of Neostigmine Injectable Products

Nationally estimated number of patients with an inpatient or outpatient (including ER) hospital discharge billing for neostigmine injectable products from U.S. non-federal hospitals, stratified by patient age*, from May 2013 through December 2015, cumulative

	Cumulative 5/2013-12/2015	
	Patients	%
Total Neostigmine Injectable	14,783,571	100.0%
0 - 16 years	653,730	4.4%
17+ years	14,132,271	95.6%

Source: IMS Health, Inpatient HealthCare Utilization System. May 2013 through December 2015. Data extracted March 2016. File: IHCARUS 2016-453 neostigmine BPCA all forms age 3-24-2016.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts.

Limitations of Drug Utilization Database

- Unable to search data by product brand
- Only focus on data from the non-federal hospital pharmacy settings
- Excludes data from Federal hospitals and VA facilities
- Excludes data from other specialty hospitals, including children's and other standalone specialty hospitals

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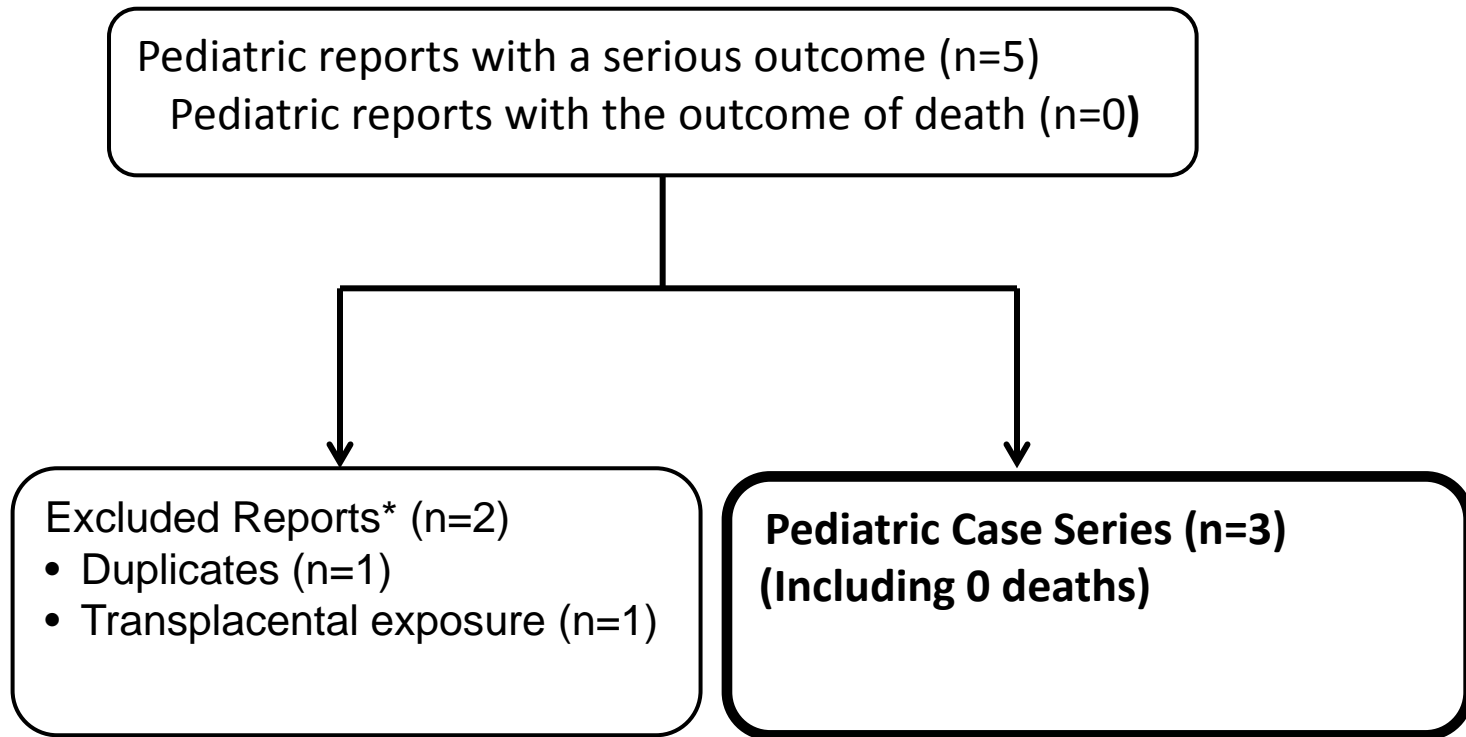


Number* of Adult and Pediatric FDA Adverse Event Reporting System (FAERS) Reports with Neostigmine (May 31, 2013 to March 29, 2016)

	All reports (US)	Serious[†] (US)	Deaths (US)
Adults (≥ 17 yrs.)	54 (21)	53 (20)	4 (2)
Pediatrics (0- <17 yrs.)	5 (0)	5 (0)	0(0)

* May include duplicates and transplacental exposures; cases have not been assessed for causality
†Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

Selection of Pediatric FAERS Cases Neostigmine



* These 2 reports were reviewed and excluded from the case series.

Serious Unlabeled Non-Fatal Adverse Events Neostigmine (n=3)

A 1 year old male undergoing diagnostic laparoscopy, open orchidopexy and circumcision developed pink frothy secretions in the endotracheal tube and coarse crepitations in all lung fields after neuromuscular blocker reversal with neostigmine. A diagnosis of pulmonary edema was made and extubation was delayed. He was treated with reparation, furosemide, hydrocortisone and ventilation. He recovered and was discharged on post-op day 2.

A 1 year old male with congenital cataracts undergoing vitrectomy and lens reconstruction developed a large amount of pink-colored foamy secretions during endotracheal aspiration after neuromuscular blocker reversal with neostigmine. Chest x-ray revealed diffused infiltrative shadows in both lung fields. The patient was diagnosed with pulmonary edema. He was treated with furosemide and sedated ventilation, and he recovered.

*Unlabeled adverse events are underlined.

Serious Unlabeled Non-Fatal Adverse Events Neostigmine (n=3) continued

A 9 year old male with chronic tonsillitis undergoing a tonsillectomy experienced tachypnea, restlessness and a wet cough with pink frothy sputum consistent with pulmonary edema after neuromuscular blocker reversal with neostigmine and extubation. Chest auscultation showed bilateral crepitations. He was reintubated and given hydrocortisone, dexamethasone, theophylline, furosemide and vecuronium. His condition improved. He was given neostigmine a second time and again experienced pink frothy secretions and had bilateral crepitations. He was treated with aminophylline, chlorpheniramine and theophylline and he recovered.

*Unlabeled adverse events are underlined.

Additional Cases of Pulmonary Edema Neostigmine (n=2)

There were two FAERS cases with pulmonary edema reported prior to May 31, 2013 (labeling date).

A 16 year old male with Brugada syndrome undergoing implantation of a cardioverter defibrillator experienced laryngeal spasm and excessive pink frothy sputum after neuromuscular blocker reversal with neostigmine and extubation. Chest radiograph confirmed pulmonary edema. He was treated with positive airway ventilation and diuretics, and he recovered.

A 6 year old male undergoing a corneal repair developed chest crepitations after neuromuscular blocker reversal with neostigmine and extubation. He was reintubated and copious pink frothy secretions were seen consistent with pulmonary edema. He was given steroids, theophylline and furosemide, and he recovered.

*Unlabeled adverse events are underlined.

Serious Unlabeled Non-Fatal Adverse Events Neostigmine

A temporal relationship between neostigmine and pulmonary edema was seen; however all five cases were confounded by potential airway management difficulties and two cases were confounded by prior respiratory or cardiac issues. These five cases were all based on literature reports.

In addition, we identified two literature reports of non cardiogenic pulmonary edema in adults post-neostigmine administration. As with the 5 cases in children, these cases occurred in surgical patients.

Summary of Safety Reviews

Bloxiverz™ (neostigmine methylsulfate)

- This concludes the pediatric focused safety review of FAERS reports.
- There are reports of pulmonary edema after administration of neostigmine.
- Due to the rarity of reports and confounding, FDA will continue routine, ongoing postmarketing safety monitoring.
- Does the committee concur?



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