



Pediatric Focused Safety Review Precedex™ (dexmedetomidine) Pediatric Advisory Committee Meeting April 12, 2016

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Outline

- **Background Information**
- Pediatric Studies
- Labeling Changes
- Drug Use Trends
- Safety
- Summary

Background Drug Information Precedex™ (dexmedetomidine)

- **Drug:** Precedex™ (dexmedetomidine)
- **Formulation:** injection
- **Sponsor:** Hospira
- **Original Market Approval:** December 17, 1999
- **Therapeutic Category:** Selective alpha₂-adrenergic agonist
- Information related to studies in pediatric patients added to the labeling in June 2013 initiated this safety review.

Background Drug Information, continued

Precedex™(dexmedetomidine)

Adult Indications

- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting not to exceed 24 hours.
- Sedation of non-intubated patients prior to and/or during surgical and other procedures.

There are no pediatric indications.

Background Drug Information, continued

Precedex™(dexmedetomidine)

Contraindications (section 4)

None

Warnings and Precautions (section 5)

- Drug Administration
 - only administered in intensive care or operating room setting.
- Hypotension, Bradycardia and Sinus Arrest
- Transient Hypertension
- Arousability
 - some patients receiving Precedex have been observed to be arousable and alert when stimulated.
- Withdrawal
 - adverse events associated with withdrawal of Precedex (e.g. nausea, vomiting and agitation)

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Pediatric Studies

Precedex™ (dexmedetomidine)

One assessor-blinded trial in pediatric patients and two open label studies in neonates were conducted to assess efficacy for ICU sedation. These studies did not meet their primary efficacy endpoints and the safety data submitted were insufficient to fully characterize the safety profile of Precedex for this patient population.*

These are the studies that initiated today's safety review.

*June 2013 labeling update

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Pediatric Labeling Changes

Precedex™ (dexmedetomidine)

8.4 Pediatric Use

- Description of the studies conducted and a statement that the use of Precedex for procedural sedation in pediatric patients has not been evaluated*

*June 2013 labeling update

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Drug Utilization Data: dexmedetomidine

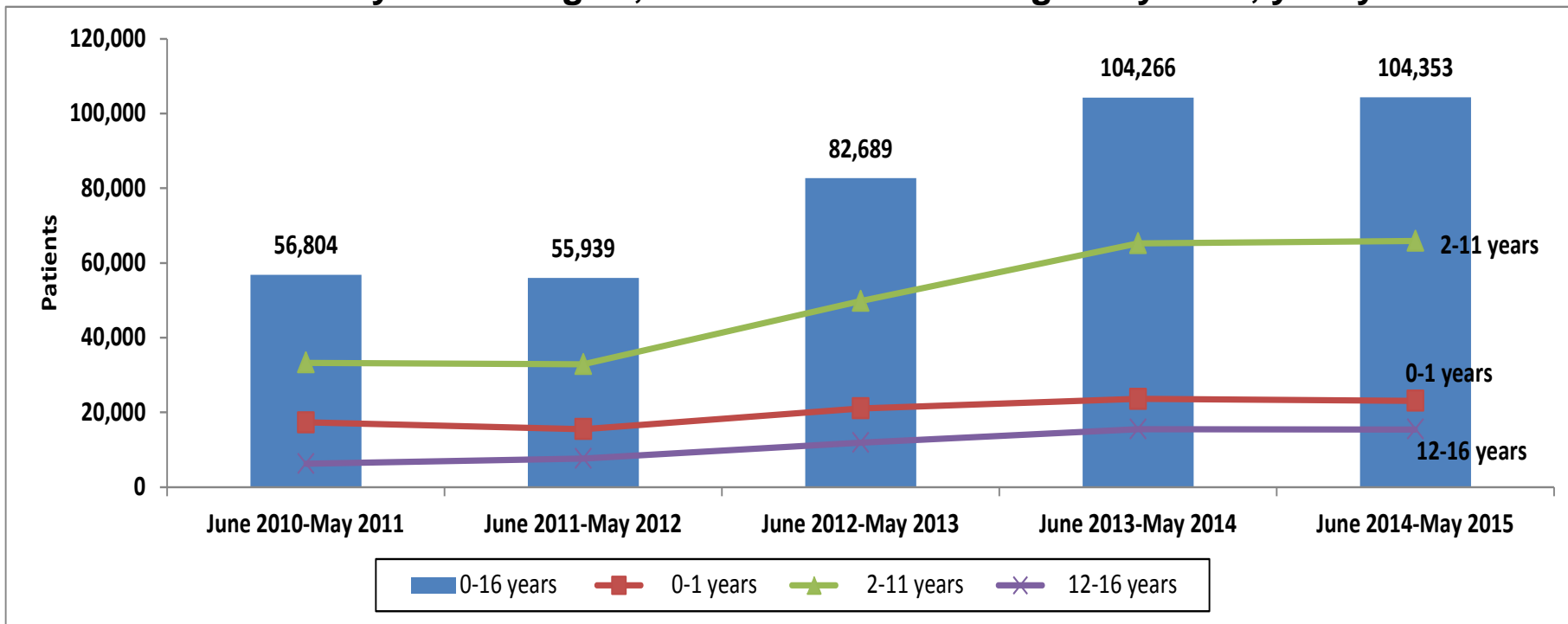
Nationally Estimated Number of Patients with Inpatient and Outpatient Billing for Dexmedetomidine HCl Injection from U.S. Non-Federal Hospitals, from June 2014 through May 2015

	June 2014-May 2015	
	Patients	Share
	N	%
Total Patients	571,019	100%
0-16 years	104,353	18.3%
0-1 years	23,082	22.1%
2-11 years	65,852	63.1%
12-16 years	15,419	14.8%
17+ years	466,666	81.7%

Source: IMS Health, Inpatient Healthcare Utilization System (IHCARUS). June 2014-May 2015. Data extracted Nov 2015.

Pediatric Drug Utilization: dexmedetomidine

Nationally Estimated Number of Pediatric Patients* (0-16 years) with Inpatient and Outpatient Billing for Dexmedetomidine HCl Injection from U.S. Non-Federal Hospitals, Stratified by Patient Age**, from June 2010 through May 2015, yearly



*Patient age groups are inclusive of all patients up to the day before their next birthday

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

Source: IMS Health, Inpatient Healthcare Utilization System (IHCARUS), Extracted NOV2015.

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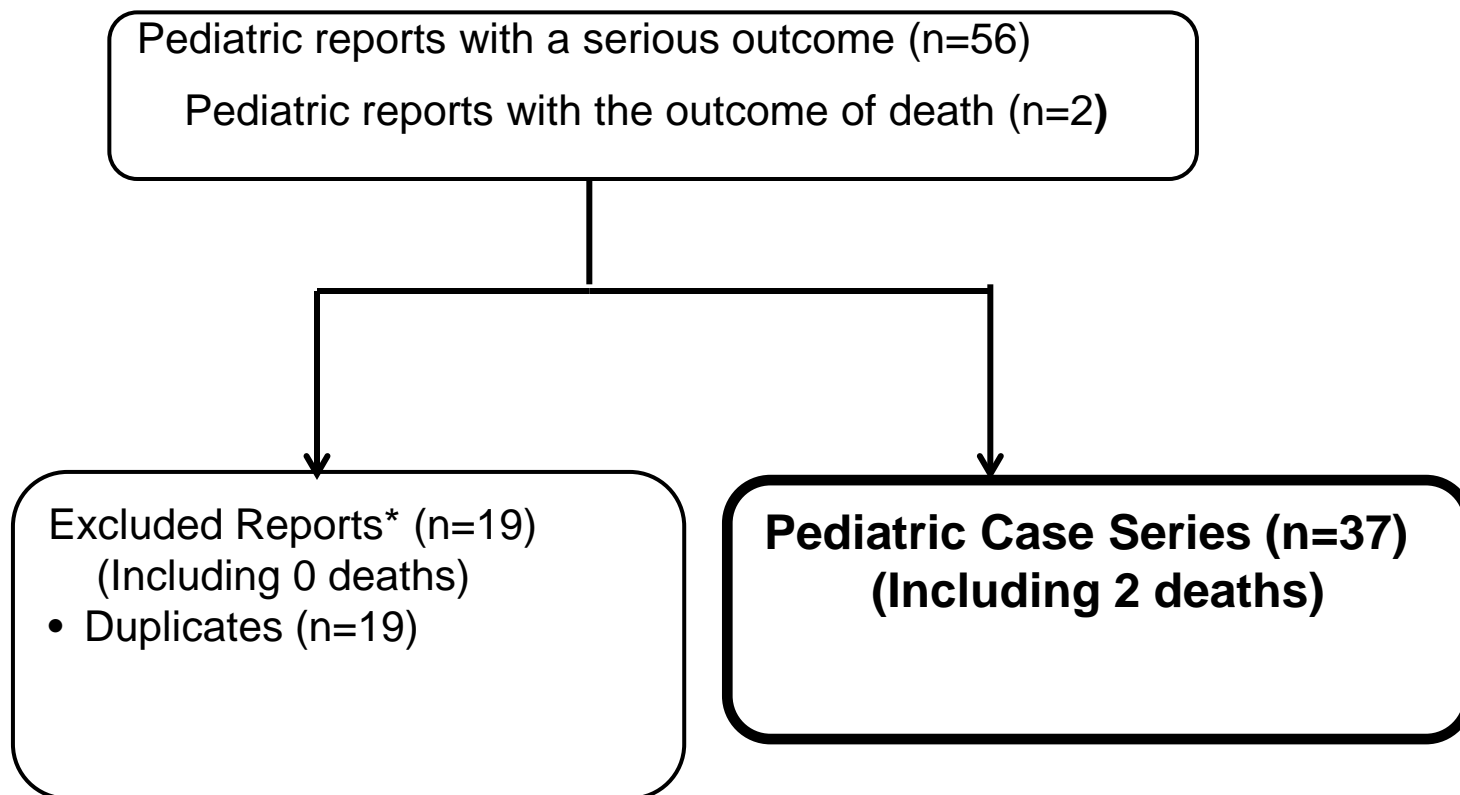
Number* of Adult and Pediatric FDA Adverse Event Reporting System (FAERS) Cases with Precedex™ (December 17, 1999 to May 31, 2015)

	All reports (US)	Serious [†] (US)	Deaths (US)
Adults (≥ 17 yrs.)	362 (123)	321 (107)	51 (16)
Pediatrics (0- <17 yrs.)	69 (29)	56 (25)	2(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



* These 19 reports were reviewed and excluded from the case series for the stated reasons.

Characteristics of Pediatric Case Series Precedex™ (dexmedetomidine)

Characteristics of Pediatric Case Series with Dexmedetomidine (N=37)

Age	0 - <1 month	4
	1 month - <2 years	13
	2 - <6 years	5
	6 - <12 years	10
	12 - <17 years	5
Indication	Sedation (n=34)	
	Ventilated	18
	Non-ventilated	8
	Procedural	6
	Post-surgical sedation	2
	Unknown ventilation status	8
	Other (n=3)	
	Pain	1
	Seizure control	1
	Unintended administration	1
Duration of Infusion	Short-term (≤24 hrs)	13
	Long-term (>24 hrs)	14
	Unknown	8

Fatal cases Precedex™ (n=2)

- A 10 year old female with history of Rett's syndrome and scoliosis surgery received a dexmedetomidine infusion on Day 1 (unknown dose, unknown indication). Within 20-30 minutes after the start of the infusion, she experienced severe hypotension and bradycardia. Dexmedetomidine was discontinued. She was given cardiac resuscitation, but died on Day 4.
- This death was possibly related to dexmedetomidine; however, her history of Rett's syndrome, which can include cardiac arrhythmias, and unknown concomitant medications were confounders.

Fatal cases Precedex™ continued (n=2)

- A 15 day-old male was born at 24 weeks gestational age with low birth weight, hyaline membrane disease, bronchopulmonary hemorrhage, patent ductus arteriosus, intracranial hypertension, intraventricular hemorrhage, septic shock (*Staph*), renal failure, seizures, and cholestasis began receiving dexmedetomidine for sedation one day prior to death. The next day cardiac ultrasound showed reduced cardiac flow, bradycardia, left ventricular hypertrophy (interventricular septum = 3 mm), diastolic dysfunction, and evidence of hypertrophic myocarditis. He then died. Autopsy findings reported the following drug levels [dexmedetomidine=6.2 ng/mL (reported as “3x above” expected), sufentanil=8.7 ng/mL, and ‘levopromazine’=491 ng/mL] and findings consistent with his underlying prematurity and known pathologies.
- The dexmedetomidine level was elevated; however, the patient’s significant morbidity and exposure to other medications were confounders.

Serious Non-Fatal Adverse Events† Precedex™ (dexmedetomidine) (n=35)

Cardiovascular (n=16)

- Syncope (n=3)
- Cardiac failure (n=2)
- Torsade de pointes (n=1)
- Cardiac arrest (n=4)
- Bradycardia (n=1)
- QT prolongation* (n=2)
- Tachycardia (n=2)
- Supraventricular tachycardia (n=1)

*QT prolongation is considered labeled for the purposes of this review since it is included in the dexmedetomidine HQ Specialty Pharma labeling.

†Unlabeled events are underlined.

Serious Non-Fatal Adverse Events† **Precedex™ (dexmedetomidine) (n=35)**

Neuropsychiatric (n=10)

- Encephalopathy (n=2)
- Cerebral infarction (n=1)
- Convulsion (n=4)
- Communication/speech disorder (n=2)
- Psychosis (n=1)

†Unlabeled events are underlined.

Serious Non-Fatal Adverse Events† Precedex™ (dexmedetomidine) (n=35)

Medication Errors and related clinical event (n=3)

- Errors include overdose and unintentional administration
- Hypoglycemia (n=1)
- Sedation (n=1)
- Bradycardia (n=1)

Hypersensitivity (n=2)

- Drug reaction with eosinophilia and systemic symptoms (n=1)
- Anaphylactic reaction (n=1)

†Unlabeled events are underlined.

Serious Non-Fatal Adverse Events[†] Precedex™ (dexmedetomidine) (n=35)

Other (n=4)

- Hepatitis fulminant (n=1)
- Hypothermia (n=1)
- Adrenal insufficiency (n=1)
- Upper airway obstruction (n=1)

[†]Unlabeled events are underlined.

Summary of Safety Reviews

Precedex™ (dexmedetomidine)

- This concludes the pediatric focused safety review of FAERS reports.
- No new safety signals were identified.
- FDA recommends continuing routine, ongoing post-marketing safety monitoring.
- Does the committee concur?

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