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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Precedex (dexmedetomidine HCl injection)
Pediatric Labeling Approval Date:	April 26, 2013
Application Type/Number:	NDA 021038
Applicant/Sponsor:	Hospira
OSE RCM #:	2015-2044

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated post-marketing adverse event reports with a serious outcome and drug utilization data for Precedex (dexmedetomidine HCl injection, referred to as "DEX" in this review) in pediatric patients.

Precedex was first approved in 1999 and is indicated for intensive care unit (intubated and mechanically ventilated patients) and procedural sedation (non-intubated patients) in adults. There is no approved indication for pediatrics.

In the hospital setting, our drug use analysis found that pediatric patients (0-16 years old) accounted for approximately 13%-19% of total patients a year with a hospital billing for DEX injection from June 2010 through May 2015. Patients aged 2-11 years old accounted for the largest proportion of DEX use among the pediatric age groups.

We found 37 pediatric serious FDA Adverse Event Reporting System (FAERS) cases with DEX. More than half (22/37) were <6 years-old, and 13/37 were >1 month and ≤ 2 years-old. Two of the 37 cases were fatal, and although the cases were confounded by concurrent disease, DEX administration could have been a contributing factor in the deaths. Almost one-half (n=16; 43%) of the cases had a cardiovascular (CV) event; the next most common event was neuropsychiatric (NPS; n=10; 29%). The most common CV events were the labeled events cardiac arrest (n=4) and the unlabeled event syncope (n=3). The most common NPS events were the labeled events of convulsion (n=4) and communication disorder (n=2) and the unlabeled event of encephalopathy (n=2).

We do not consider the unlabeled events to be new safety signals because of related information in existing labeling and/or confounding factors identified in each report. The labeled events are consistent with existing labeling. Thus, there is no evidence from these data that there are new pediatric safety concerns with DEX at this time.

We recommend routine pharmacovigilance monitoring for DEX.

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1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Precedex (dexmedetomidine HCl injection, also referred to as "DEX" in this review) was approved for adults on 12/17/99. Current indications (as of 11/14/14 label revision) include sedation of 1) initially intubated and mechanically ventilated patients during treatment in an intensive care setting and 2) non-intubated patients prior to and/or during surgical and other procedures. Precedex is not indicated for infusions lasting longer than 24 hours and is not indicated for use in pediatrics. Recommended dosing for adults includes the following: 1 mcg/kg over 10 min (loading dose for ICU and procedural sedation); 0.2 to 0.7 mcg/kg/hr (maintenance dosing for ICU sedation); and 0.6 mcg/kg/hr, titrated to clinical effect, with doses ranging from 0.2 to 1 mcg/kg/hr (maintenance dosing for procedural sedation).

On June 17, 2013, information on three pediatric studies (one assessor blinded-trial in pediatric patients and two open label studies in neonates that assessed efficacy of Precedex for ICU sedation) was added to the Precedex labeling. This information, included in the Pediatric subsection of the Use in Specific Populations section, is further detailed here:

> Safety and efficacy have not been established for Procedural or ICU Sedation in pediatric patients. 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. The use of Precedex for procedural sedation in pediatric patients has not been evaluated.

1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

Currently there are two DEX products that have been approved through the NDA process.[1] Precedex (NDA 021038) was the innovator product approved in 1999, and dexmedetomidine-HQ Specialty (NDA 206628) was recently approved in October 2015. On May 4, 2015 the Division of Pharmacovigilance (DPV) completed a FDA Adverse Event Reporting System (FAERS) and literature review of DEX to support the Division of Anesthesia, Analgesia, and Addiction Product's (DAAAP's) review of an NDA submission (206628, HQ Specialty).[2] Based on the consult request from DAAAP, the DPV review focused on five different event/event groups: 1) fatalities reporting brain injury, bradycardia, or hypotension; 2) QT prolongation, including torsades de pointes; 3) hypernatremia; 4) epileptic seizures; and 5) rash. DPV recommended labeling changes as shown in Table 1.2.

Table 1.2. DPV Recommended Labeling Changes from HQ Specialty Consult

Label Section	Modification
5.2 Warnings: hypotension, bradycardia, and sinus arrest	Mention that hypotension and bradycardia can be *fatal*
6.2 Adverse Reactions: Postmarketing Experience	
Heart Rate and Rhythm Disorders	add QT prolongation

[1] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; accessed 2/19/16. In addition, there are four approved generic DEX products (Akorn, Accord, Mylan and Fresenius) and three tentatively approved generic DEX products (Par, Sandoz and Sun Pharm).

[2] Pollock M. Postmarket-safety review: dexmedetomidine and select events. OSE RCM# 2014-2063. The HQ Specialty product contains two preservatives (methylparaben and propylparaben) and is only indicated for procedural (non-intubated) sedation.

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Table 1.2. DPV Recommended Labeling Changes from HQ Specialty Consult	
Renal Disorders	add polyuria
Metabolic and Nutritional Disorders	add hypernatremia
Skin and Appendages Disorders	add pruritus, rash, urticaria

NDA 206628 was approved on 10/21/2015, and DAAAP incorporated DPV's labeling recommendations into the dexmedetomidine HQ Specialty labeling.

1.3 SUMMARY OF LABELED SAFETY ISSUES

The following text appears in the *Highlights* section of the Precedex labeling:

---------- CONTRAINDICATIONS ----------

None.

---------- WARNINGS AND PRECAUTIONS ----------

- Monitoring: Continuously monitor patients while receiving Precedex.
- Bradycardia and Sinus Arrest: Have occurred in young healthy volunteers with high vagal tone or with different routes of administration, e.g., rapid intravenous or bolus administration.
- Hypotension and Bradycardia: May necessitate medical intervention. May be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in the elderly. Use with caution in patients with advanced heart block or severe ventricular dysfunction.
- Co-administration with Other Vasodilators or Negative Chronotropic Agents: Use with caution due to additive pharmacodynamic effects.
- Transient Hypertension: Observed primarily during the loading dose. Consider reduction in loading infusion rate.
- Arousability: Patients can become aroused/alert with stimulation; this alone should not be considered as lack of efficacy.
- Prolonged exposure to dexmedetomidine beyond 24 hours may be associated with tolerance and tachyphylaxis and a dose-related increase in adverse events.

---------- ADVERSE REACTIONS ----------

- The most common adverse reactions (incidence greater than 2%) are hypotension, bradycardia, and dry mouth.
- Adverse reactions associated with infusions greater than 24 hours in duration include ARDS, respiratory failure, and agitation.

---------- DRUG INTERACTIONS ----------

Anesthetics, Sedatives, Hypnotics, Opioids: Enhancement of pharmacodynamic effects. Reduction in dosage of Precedex or the concomitant medication may be required.

Appendix A of this document includes additional text for selected *Warnings* and text from the *Drug Interactions* (Section 7.1) and *Drug Abuse and Dependence* (Section 9.3) sections.

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Most of the *Warnings* describe the risk of cardiovascular adverse events, such as serious events of bradycardia, hypotension and sinus arrest.[3] The *Warnings* also mention hypertension (during the loading dose) and hypertension and tachycardia (in the context of withdrawal).

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. See Appendix B for detailed descriptions of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for Precedex (dexmedetomidine HCl) for 2014. Sales data for dexmedetomidine HCl by the number of vials sold from the manufacturer to all U.S. channels of distribution showed that approximately 99.95% of dexmedetomidine HCl vials were distributed to non-retail pharmacies (primarily non-federal hospitals), and less than 1% were to outpatient retail settings and mail-order/specialty pharmacies.[4] As a result, only non-retail pharmacy utilization patterns were examined for dexmedetomidine HCl. Mail-order/specialty pharmacy and outpatient retail pharmacy settings data were not included in this analysis.

2.1.2 Data Sources Used

The IMS Health, Inpatient Healthcare Utilization System (IHCarUS) database was used to obtain the nationally estimated number of patients who had a hospital discharge billing for dexmedetomidine HCl injection, from the non-federal hospital inpatient and outpatient hospital settings from June 2010 through May 2015, by 12-month periods or moving annual total (MAT), stratified by patient age (0-1, 2-11, 12-16, and 17 years and older).

2.2 RESULTS

2.2.1 Unique Patients

Table 2.2.1 below provides the nationally estimated number of patients with a hospital billing for dexmedetomidine HCl from U.S. non-federal hospitals, stratified by patient age (0-1, 2-11, 12-16, 17 years and older) from June 2010 through May 2015. During the examined time period, the number of patients billed for dexmedetomidine HCl increased from approximately 316,000 patients in 12-month time period ending in May 2011 to approximately 571,000 patients in 12-month period ending in May 2015. In the most recent 12-month period ending in May 2015, the adult population aged 17 years and older accounted for 82% (467,000 patients) of total patients billed for dexmedetomidine HCl and pediatric patients aged 0-16 years accounted for 18% (104,000 patients) of total patients. Among the pediatric population, patients aged 2-11 years accounted for the largest proportion of use at 63% (66,000 patients), followed by patients aged 0-1 years at 22% (23,000 patients) of patients. Patients aged 12-16 years accounted for 15% (15,000 patients) of pediatric patients.

[3] 'Cardiac arrest' is mentioned in *Adverse Reactions*/Postmarketing Experience (Section 6.2, Table 7).
[4] Source: IMS Health, IMS National Sales Perspectives™, Jan 2014-Dec 2014. Extracted Sept 2015.
File: NSP 2015-2044 Precedex by Superchannels for 2014, 9-23-15 xlsx.

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Table 2.2.1 Nationally Estimated Number of Patients* 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**

	June 2010-May 2011		June 2011-May 2012		June 2012-May 2013		June 2013-May 2014		June 2014-May 2015	
	Patients N	*Share %*	Patients N	*Share %*	Patients N	*Share %*	Patients N	*Share %*	Patients N	*Share %*
Total Patients	**316,205**	***100%***	**409,020**	***100%***	**519,650**	***100%***	**542,881**	***100%***	**571,019**	***100%***
0-16 years	**56,804**	***18.0%***	**55,939**	***13.7%***	**82,689**	***15.9%***	**104,266**	***19.2%***	**104,353**	***18.3%***
0-1 years	17,315	*30.5%*	15,526	*27.8%*	21,077	*25.5%*	23,586	*22.6%*	23,082	*22.1%*
2-11 years	33,253	*58.5%*	32,828	*58.7%*	49,769	*60.2%*	65,223	*62.6%*	65,852	*63.1%*
12-16 years	6,236	*11.0%*	7,586	*13.6%*	11,843	*14.3%*	15,457	*14.8%*	15,419	*14.8%*
17+ years	**259,401**	***82.0%***	**353,081**	***86.3%***	**436,960**	***84.1%***	**438,615**	***80.8%***	**466,666**	***81.7%***
Unspecified	**0**	***0%***	**0**	***0%***	**0**	***0%***	**0**	***0%***	**0**	***0%***

Source: IMS Health, Inpatient Healthcare Utilization System (IHCarUS). June 2010-May 2015. Data extracted Nov 2015. File: Precedex Adhoc Nov 18 2015 use by age.xlsx.

*Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study nor across patient age subtotals due to patients aging during the study. Patients may be counted more than once in the individual age categories. Therefore, summing across time periods or across patient age bands is not advisable and may result in overestimates of patient counts.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-16 years of age includes patients 16 years and 11 months

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix C for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	8/31/15
Time Period of Search	12/17/99-5/31/15*
Search Type	FBIS Quick Query
Product Name(s)	Dexmedetomidine, Dexmedetomidine hydrochloride
Search Parameters	All ages, all outcomes, worldwide

*12/17/99 is the date of initial approval of Precedex and 5/31/15 was the most recent drug use data available.

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3.2 RESULTS

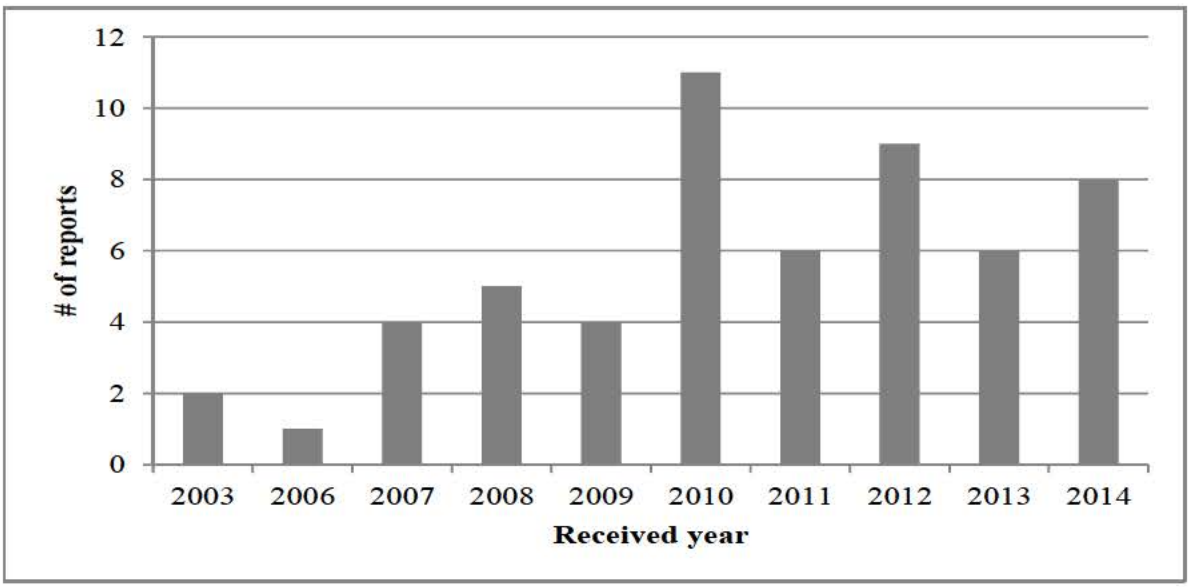
3.2.1 Total Number of FAERS Cases by Age

Table 3.2.1 Total Adult and Pediatric FAERS Cases from 12/17/99 to 5/31/15 with Dexmedetomidine*

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	362 (123)	321 (107)	51 (16)
Pediatrics (0 - <17 years)	69 (29)	56‡ (25)**	2‡ (0)

* May include duplicates and transplacental exposures, and 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.
‡See Figure 3.2.2

Figure 3.2.1 Serious Pediatric Reports for Dexmedetomidine, by year of initial FDA receipt (2/17/99-5/31/15; n=56)



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 56 pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

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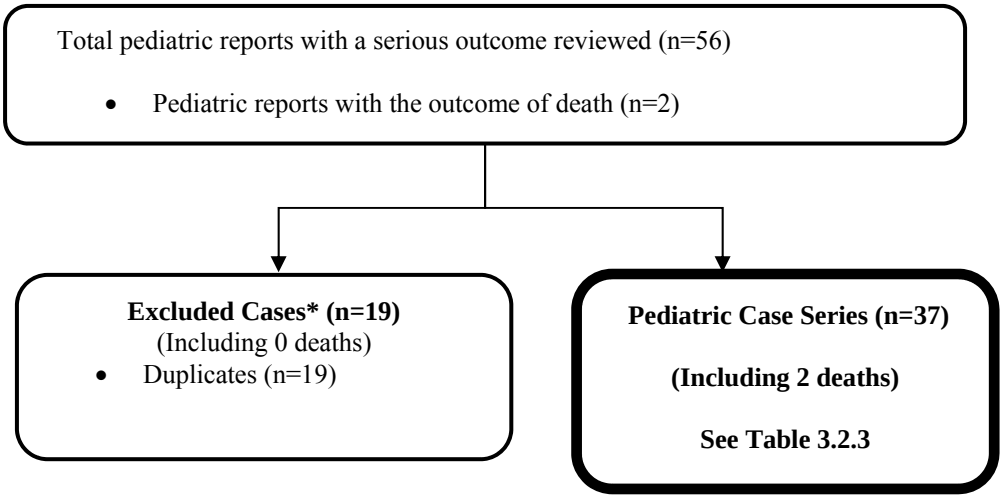
Figure 3.2.2 Selection of Serious Pediatric Cases with Dexmedetomidine



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.

3.2.3 Characteristics of Pediatric Case Series

Appendix D lists all the FAERS case numbers, FAERS version numbers, Manufacturer Control Numbers and other information for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Dexmedetomidine (N=37)

Age (n=37)	0 - < 1 month	4		
	1 month - <2 years	13		
	2- < 6 years	5		
	6- <12 years	10		
	12- < 17 years	5		
Sex	Male	15		
	Female	19		
	Unknown	3		
Country	US	20		
	Foreign	17		
Indication				
Sedation (n=34)				
	Ventilated		18	
	ICU			16
	Operating room			2
	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 (n=35)*	Short-term (≤ 24 hrs)	13		
	Long-term (> 24 hrs)	14		
	Unknown	8		

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Table 3.2.3 Characteristics of Pediatric Case Series with Dexmedetomidine (N=37)		
Serious Outcome†	Death	2
	Life-threatening	8
	Hospitalized	14
	Disability	2
	Congenital anomaly	0
	Other serious	20

[#] Medical imaging (n=4), cardiovascular catheterization (n=1), unknown (n=1).
*Excluding one case of nasal administration and one case of unintentional bolus administration.
† 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. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

In the first case (10 year-old) the death was possibly related to DEX; however, the patient's prior cardiac-related history and unknown concomitant medications were confounders. In the second case (15 day-old), even though the DEX level was high, the patient's significant morbidity and exposure to other medications were confounders.

FAERS Case ID 7418166. A 10 year-old female with history of Rett's syndrome[5] and scoliosis surgery received a DEX infusion (unknown dose[6]) on Day 1 for an unknown indication; concomitant medications were not reported. Within 20-30 minutes after the start of the DEX infusion, she experienced severe hypotension and bradycardia. DEX was discontinued on Day 1. The patient was given cardiac resuscitation, but died on Day 4.

FAERS Case ID 10551376. A 15 day-old male, born premature at 24 weeks and hospitalized since birth, was switched from midazolam to DEX for sedation on hospital day 15. Co-morbidities included low birth weight, hyaline membrane disease, bronchopulmonary hemorrhage, patent ductus arteriosus, intracranial hypertension, intraventricular hemorrhage, septic shock (*Staph*), renal failure, seizures, and cholestasis. DEX dose was not clear; duration was not definitively stated but could have been up to 2 days. The day after DEX infusion was started, ultrasound showed 'reduced cardiac flow with bradycardia and left ventricular hypertrophy (interventricular septum was 3 mm) with diastolic dysfunction; evidence of hypertrophic myocarditis' and the patient died. At autopsy, DEX level was 6.2 ng/mL, which the reporter said was '3 times higher than expected;'[7] sufentanil (8.7 ng/mL) and 'levopromazine' (491 ng/mL) levels were also reported, both possibly indicating excessive exposure in the neonate. [8] Autopsy also mentioned

[5]Rett's syndrome is a genetic (X chromosome-linked) neurological disorder principally manifested by mental retardation. There can be autonomic abnormalities which can result in cardiac abnormalities such as prolonged QT interval. Weng SM, Bailey ES, Cobb SR. Rett syndrome: from bed to bench. Pediatr Neonatol. 2011;52:309-316.
[6]In Sections 3.3 and 3.4 of this review, we will mention DEX dosing if 1) it was not reported or 2) if the reported dosing was higher than the approved adult dosing (see Section 1.1).
[7]DEX labeling (as of 11/14/14) shows plasma levels (adults) of 0.27-1.37 ng/mL where dosing was loading: 0.5-2.2 mcg/kg and maintenance: 0.17-0.7 mcg/kg/hr.
[8]Levomepromazine (LMZ), also known as methotrimeprazine, is a phenothiazine with analgesic and anti-emetic activity. LMZ is not approved in the US. The neonate's LMZ (as well as sufentanil) exposure was *perinatal* as the medications were given to the neonate's mother during a Cesarean section. The neonate's LMZ level appears to be higher than the 26 ng/mL that has been reported for a 25 mg intramuscular dose in an adult (Dahl SG. Pharmacokinetics of methotrimeprazine after single and multiple doses. Clin Pharmacol Ther. 1976;19:435-42). Sufentanil (Sufenta) labeling (revised 3/20/14) states: 'After epidural

factors related to the patient's death as 'organ failure and bradycardia, extreme prematurity with several complications [of] acute bronchopneumopathy with hyaline membrane disease, pulmonary lobule disorder, perforated bowel necrosis, patches of liver necrosis.'

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=35)

There were 35 non-fatal serious cases with most (n=29; 83%) reporting multiple events. In order to have mutually exclusive grouping, we classified each case based upon a key event.[9] We then determined the labeling status of the key events. We use 'labeled' to be explicit where there is an exact term or implicit where there is a similar term(s) in the DEX (Precedex) labeling. Appendix E lists the labeled events and the relevant locations in the labeling where the explicit or implicit terms are found. Almost three-quarters (n=25; 71%) of the non-fatal cases were also published in the medical literature (see Table 3.4).

Table 3.4 Non-Fatal Serious Cases: Event Category and Labeling Status

Event Category	Total	Unlabeled	Labeled
Cardiovascular	16 (11)†	6	10
Neuropsychiatric	10 (6)	3	7
Hypersensitivity	2 (2)	2	
Other event	4 (3)	3	1
Medication error	3 (3)		3
Total	35 (25)	14	21

†Value in parentheses is number of FAERS cases also published in the medical literature.

3.4.1 *Cardiovascular (n=16)*

Table 3.4.1 shows the cardiovascular event cases with the labeling status of the key event.

Table 3.4.1 Cardiovascular Cases and Labeling Status

Event	Unlabeled	Labeled
Syncope	3	
Cardiac failure	2	
Torsade de pointes	1	
Cardiac arrest		4
Bradycardia		1
QT prolongation*		2
Tachycardia†		2
Supraventricular tachycardia†		1

administration of incremental doses totaling 5 to 40 mcg sufentanil during labor and delivery, maternal and neonatal sufentanil plasma concentrations were at or near the 0.05 to 0.1 ng/mL limit of detection, and were slightly higher in mothers than in their infants.'

[9]When there was more than related event, we chose the term that connoted the most morbid condition (e.g., *cardiac arrest* over *bradycardia).*

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Table 3.4.1 Cardiovascular Cases and Labeling Status		
Total	6	10

* QT prolongation was considered labeled for the purpose of this OSE review, as it is included in the dexmedetomidine HQ Specialty Pharma labeling (rev. 10/2015). Refer to Section 1.2 of this review.
†May be related to DEX drug withdrawal.

Unlabeled (n=6)

Three cases of **syncope** occurred in an 8, 11 (*Patel* lit) and 14 year-old, all after DEX was discontinued for medical imaging procedures. Syncope-occurrence was a few hours after DEX administration (8 year-old), when the patient got up to use restroom (11 year-old), and 30 minutes after discharge approval (120 min after DEX bolus administration; 14 year-old). At the time of the event, all had bradycardia; the 8 year-old also had hypotension and a seizure, but had a normal heart rate (70 bpm) a half-hour before the event. The 11-year old received DEX (2.4 mcg/kg) via the unapproved intranasal route. Confounding factors included asthma[10] (11 year-old) and concomitant propofol administration (14 year-old); confounding factors were not reported for the 8 year-old. All patients recovered.

The two **cardiac failures** were in ICU patients aged 3 months (*Gupta* lit) and 1 year (*Shiba* lit) with history of congenital heart defects for which surgery was performed. DEX infusions were long-term (≥ 4 days) with unknown and concomitant sedatives (midazolam and fentanyl). Both patients recovered. Event occurrence for the 3 month-old was during DEX administration, resulting in discontinuation. The 1 year-old first had tachycardia (170 bpm) 6 hours *after* DEX discontinuation, which subsequently progressed to cardiac failure. DEX was initially given at 1 mcg/kg/hr and subsequently reduced to 0.4 mcg/kg/hr. The reporter (*Shiba* lit) claimed that the cardiac failure was due to 'DEX withdrawal.' While tachycardia in the setting of withdrawal is described in labeling (Appendix A), the patient's hypoplastic left heart syndrome may have been a contributing factor for the cardiac failure.

The **torsades de pointes case** was an 8 month-old who was being weaned from fentanyl and midazolam. She experienced ventricular arrhythmia and torsades de pointes 6 hours post DEX infusion (unknown dose) for 'transient sedation.' The case is confounded by her respiratory syncytial virus infection and unknown status of other medications and medical history.

Labeled (n=10)

The five cases of **cardiac arrest** (n=4) **and bradycardia** (n=1) were in patients aged 1 month to 15 years (median 3 years). All had a positive dechallenge, and all recovered.

> Most were ICU patients (n=4) and one was post-cardiac surgery, not otherwise specified (NOS). Two cases had a short-term DEX infusion (≤24 hours). All five cases had other factors that could have contributed to the cardiac events [e.g., congenital heart disease (*Shepard* lit), other anesthetics (*Bharati* lit)]. One of these cases (cardiac arrest in a 12 year-old) had a pre-existing intracranial hemorrhage, and although the cardiac arrest resolved after DEX discontinuation, bradycardia and

[10]The patient's asthma may have affected DEX delivery via intranasal route.

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hypotension continued. The maintenance DEX dose (1 mcg/kg/hr) in one of the cardiac arrest cases (2 year-old with chest injury post auto accident) exceeded recommended adult dosing for ICU sedation. In the bradycardia case (1 month-old, *Berkenbosch* lit) with an atrioventricular septal defect, the reporter said that the bradycardia may have resulted from 'increase[d] vagal tone' due to a DEX-digoxin interaction.

There were two cases of **tachycardia,** both 3 months-old (*Yamamoto* lit and *Hagushi* lit), and one case of **supraventricular tachycardia,** 5 months-old **(***Yamamoto* lit). DEX was administered post-septal defect surgery (*Yamamoto* lit) and to wean off mechanical ventilation (*Hagushi* lit). Tachycardia occurred after DEX discontinuation in all cases. Time from DEX discontinuation to event onset was 3-6 hours (both 3 month-olds) and unknown for the 5 month-old. DEX dosage was unknown for the 3 month-old (*Hagushi* lit) and the 5 month-old. Concomitant medications were unknown. Tachycardias were both >200 bpm. Although information is limited, the tachycardias appear to be related to *DEX withdrawal.*

The patients with **QT prolongation** were 8 (*Matras* lit) and 22 (*Burns* lit)-months old. They both received DEX in the ICU and had event onsets of 4 days and 4 hours, respectively. DEX duration was 4 days and 20 hours, respectively; both had positive dechallenges. Contributing factors were other medications[11] and hypokalemia (8 month-old) and possible long QT syndrome (22 month-old).

3.4.2 *Neuropsychiatric (n=10)*

Table 3.4.2 Neuropsychiatric Cases and Labeling Status

Event	Unlabeled	Labeled
Encephalopathy	2	
Cerebral infarction	1	
Convulsion		4†
Communication/speech disorder		2‡
Psychosis		1*
Total	3	7

†One case was myoclonus
‡May be related to DEX drug withdrawal syndrome
*Psychosis not explicitly labeled. Similar labeled terms include confusional state, delirium, hallucination, and illusion.

Unlabeled (n=3)

One **encephalopathy** case occurred in a 14-month old, admitted for a retropharyngeal abscess (had methicillin sensitive *Staph;* prior medical history was negative), who received a long-term DEX infusion (duration 5-7 days, dose was up to 1.4 mcg/kg/hr). Encephalopathy occurred after DEX discontinuation, on the same day. The reporters stated that the patient was 'acutely encephalopathic with choreathetoid movements of arms, vacant stare, lip smacking, eye flickering, decreased tone.' The patient also received fentanyl and midazolam; any tapering technique for discontinuation was not reported.

[11] *Matras* concluded that metoclopramide and haloperidol (labeled for QT prolongation) were equally likely to have contributed to the event based upon temporal relationship and published literature.

Reference ID: 3899882

The other **encephalopathy** case occurred in an 11 year-old (*Hoehn* lit), with sickle cell disease who was hospitalized for being 'in extremis with hypoxemia and shock.' The patient received a long-term DEX infusion (duration 5-7 days, dose was up to 2.5 mcg/kg/hr), and encephalopathy occurred 12 hours after DEX discontinuation. The patient was hypertensive and became 'agitated and combative, and progressed to altered mental status.' The patient was re-intubated, sedated (with DEX and fentanyl), and had two seizures; head CT was negative but MRI was 'consistent with reversible encephalopathy syndrome.' DEX and fentanyl (first regimen) were abruptly terminated; the patient was treated with intermittent fentanyl and midazolam for potential withdrawal.

Regarding both encephalopathy cases, dosing may have been a contributing factor as it was higher than recommended adult dosing. These two cases could have been related to DEX withdrawal but are confounded by medical history and/or other medications (e.g., fentanyl).

A 9 year-old (*Satou* lit) with Moyamoya disease underwent encephalo-duro-arterio-synangiosis (EDAS) surgery. DEX was started 1.5 hours before end of surgery and continued post-operatively. His extremity movement was normal right after surgery. The patient became 'restless and [experienced] a paralyzed right upper limb 14 hours after DEX started.' CT showed a 'new left **cerebral infarction**.' DEX was continued for 5 more days. The patient underwent rehabilitation; he could not move his right fingers but did improve to get 'writing ability.' Contributing factors were the patient's medical history and the EDAS surgery. The patient also received the following perioperative medications: fentanyl, propofol, remifentanyl and rocuronium. While the maintenance dose was within recommended adult dosing (0.4 mcg/kg/hr), the loading dose (1.5 mg/kg) was higher than recommended adult dosing.

Labeled (n=7)

One of the four **convulsion** cases was a 16 year-old leukemic male who was a subject in a prospective study for efficacy of DEX analgesia in patients who have experienced opioid induced hyperalgesia (OIH) (*Belgrade* lit). The subjects were in the ICU (for monitoring purposes) when they received DEX. The subject was a 'pain service patient' and had prior OIH with at least methadone and fentanyl. The patient was admitted for a cholecystectomy. He was given opioid therapy pre-operatively and morphine PCA, methadone and ketamine post-operatively. DEX was then given, and over the next couple of days, the opioids were able to be reduced. The authors stated that, 'morphine PCA was tapered down due to **myoclonus** and adequate pain control. DEX infusion was also tapered down over this time period.' The patient received DEX for at least 5 days. There were no details given about this 'induced' myoclonus and the role of DEX is not clear.

The remaining three **convulsion** cases were in patients 5 days- (*Kubota* lit) and 7 years-old (n=2; '7a' and '7b'). They all had long-term DEX infusions (43-84 hours; unknown dose for 7 year-olds). In two cases (5 day-old, 7b years-old) event onset was between 72 and 80 hours. All cases had contributing factors, which included prior seizure occurrence and/or brain injury (7a[12] and 7b years-old) and neonatal respiratory syndrome (5 day-old).

Two patients [2 years-old (*Miller* lit) and 3 years-old] experienced a **communication disorder/speech disorder** after (5 hours, unknown) discontinuation of their long-term ICU DEX infusions (duration 11, 5 days). These events were reported as 'decreased verbal communication' and 'stopped talking,'

[12]Had seizure exacerbation throughout the 43-hour infusion period.

Reference ID: 3899882

respectively. The 2 year-old was also weaned from concomitant fentanyl and midazolam via methadone and diazepam, respectively. For the 3 year-old, there was no mention of DEX tapering (dose also unknown). Both patients recovered. Other confounding factors were neuroblastoma and tetralogy of Fallot, respectively. The communication disorder/speech disorder in these two cases may have been related to withdrawal of DEX based on the temporal relationship; however, both cases are confounded by prior medical history.

The **psychosis** patient **(**14 year-old, *Ahua* lit) was being managed for accidental organophosphate poisoning. After 5 days in the ICU, her caregivers started to wean her from ventilator support. DEX was given for sedation (unknown dose) during this transitional period. She became agitated and aggressive before and after extubation and showed sudden hyperactivity, rigid posture and mutism. She had a psychiatric consult. The authors considered this a case of *ICU psychosis* caused by fluctuating consciousness levels and multiple drugs (e.g., propofol, morphine, anticholinergics) during ICU care. The patient recovered. There were many other factors besides DEX that were involved in this case of 'ICU psychosis.'

3.4.3 Hypersensitivity (n=2)

Table 3.4.3 Hypersensitivity Cases and Labeling Status

Event	Unlabeled	Labeled
Drug reaction with eosinophilia and systemic symptoms	1	
Anaphylactic reaction	1	
Total	2	0

The cases were 11- (*Shigmatsu* lit) and 16 -years-old (*Nunziata* lit) and received DEX (unknown dose) in the ICU and operating room, respectively. The cases reported 'drug induced hypersensitivity syndrome' and 'anaphylaxis.' The hypersensitivity reactions were described as a skin reaction that 'spread to the whole body' (11 year-old) and hypotension, swelling and anuria (16 year-old). DEX infusion durations were 1-2 days and less than a day, respectively. Hypersensitivity occurred one day after DEX infusion termination and within a few hours after start of DEX infusion. Both cases had non-DEX perioperative and other drugs that could have caused the hypersensitivity. The 11 year-old tested positive (DLST) for four non-DEX drugs.[13] The only testing done for the 16 year-old was latex which was negative.

[13]DLST=drug lymphocyte stimulation test. Patient was not allergy tested for DEX.

Reference ID: 3899882

3.4.4 Other (n=4)

Table 3.4.4 Other Events and Labeling Status		
Event	Unlabeled	Labeled
Hepatitis fulminant	1	
Hypothermia	1	
Adrenal insufficiency	1†	
Upper airway obstruction		1*
Total	3	1

†DEX labeling mentions a diminished ACTH-stimulated cortisol response in the Animal Pharmacology and/or Toxicology subsection of the Nonclinical Toxicology section.
* Upper airway obstruction not explicitly labeled. Similar labeled terms include respiratory failure, acute respiratory distress syndrome, apnea, dyspnea, hypoventilation, hypoxia, pulmonary congestion, and respiratory acidosis.

Unlabeled (n=3)

A case of **fulminant hepatitis** occurred in a 5 month-old who received DEX; dose and indication was unknown. The patient received a DEX infusion for a duration up to 1 day, and fulminant hepatitis occurred 2 days after DEX discontinuation. In addition to elevated transaminases, the patient had abnormal coagulation, was intubated, and received continuous hemodialysis and plasma exchange. Confounders included acetaminophen (unknown dose) and spironolactone. The patient recovered.

A case of **hypothermia** (33º C) occurred in a non-intubated 2 day-old (*Finkel* lit) who received DEX in the ICU post-bladder surgery. DEX infusion duration was 7 days, and the event onset was 9 hours after the start of DEX. Confounders included sevoflurane, ropivacaine (both labeled for hypothermia) and fentanyl (author's suggestion). The patient recovered.

The **adrenal insufficiency (**1 year-old, *Tucker* lit) occurred after discontinuation of a long-term (6.5 day) DEX infusion. DEX was started at 0.5 mcg/kg/hr and was escalated to 2.7 mcg/kg/hr. Four days after DEX discontinuation, he was lethargic, hypotensive and mildly tachycardic (112 bpm). His blood cortisol level was measured the next day and found to be low (0.4 mcg/dL).[14] He recovered 3 days later. Confounding factors were a higher than recommended DEX adult dosing, other drugs (dexamethasone and clonidine) and complications from a 2nd degree burn (patient was admitted with 24% of his body scalded from boiling water). The lack of a strong sympathetic response (e.g., hypertension and significant tachycardia) after DEX discontinuation suggests that this was not a case of DEX withdrawal.

[14]Normal range (mcg/dL): 7-25 morning, 2-14 afternoon. http://www mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8545; accessed 1/28/16.

Labeled (n=1)

A 7-year-old (*Lubisch* lit) with attention deficit hyperactivity disorder developed **upper airway obstruction** after receiving DEX (unknown dose) for a diagnostic neurologic procedure. The obstruction was relieved by placement of a nasopharyngeal airway; the procedure was able to be completed. Relevant medical history and concomitant medications were unknown.

3.4.5 Medication errors (n=3)

Table 3.4.5 Medication Error Cases and Labeling Status (for clinical event)

Event	Unlabeled	Labeled
Hypoglycemia		1
Sedation		1
Bradycardia		1
Total	0	3

A 20 (*Bernard* lit) and 21 (*Max* lit) month-old were intended to receive 1 mcg/kg/hour of DEX (within adult recommended dose) for procedural sedation. Both had their pumps *misprogrammed* to 1 mcg/kg/***min*** and received doses 60-times the intended dose. Infusions lasted 36 and 20 minutes, respectively. Both patients became 'deeply' sedated. The 20 month-old had hypoglycemia (labeled; blood glucose 26 mg/dL) 3 hours after DEX was discontinued. Her glucose level was restored (via dextrose infusion) the same day. Both patients were monitored overnight in the ICU, experienced no further sequel, were discharged the next day. Contributing factors for the 20 month-old were propofol (given before DEX) and (in the author's opinion) the patient's '[glucose] substrate deficiency', as she had no oral intake for 10 hours prior to the procedure.

A 3 year-old (*Nath* lit) hospitalized for pyogenic meningitis received a DEX overdose (9 mcg/kg bolus) as an unintentional administration (i.e., the patient's treatment plan did not include DEX). He became unconscious and had bradycardia (labeled events). He was treated with fluids and epinephrine and recovered 7 hours after DEX administration.

On February19, 2016, the DPV reviewer notified the FDA/CDER/OSE Division of Medication Error and Prevention Analysis (DMEPA) team that monitors DEX of these findings. DMEPA reviewed the 3 medication error cases and determined that no regulatory action is indicated. One foreign case described an unintentional administration and two cases involved infusion pump programming errors, which are errors not unique to this product.[15]

4 DISCUSSION

This review focused on pediatric utilization of dexmedetomidine HCl and all serious pediatric adverse events spontaneously reported with dexmedetomidine HCl. Dexmedetomidine HCl is indicated for ICU

[15] This DMEPA assessment was provided via email by the DMEPA reviewer on March 9, 2016.

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or procedural sedation for adult patients. Our drug use analyses suggested that dexmedetomidine HCl injection was used among patients of all ages including use in children (0-16 years old), which is considered off-label. Although patients aged 17 years and older accounted for the majority of dexmedetomidine HCl use from the U.S. non-federal hospital setting, approximately 13%-19% of total patients who had a hospital billing for dexmedetomidine HCl were pediatric patients (0-16 years) from June 2010-May 2015. Precedex has been on the market since 1999. Literature reviews of small studies and case reports of dexmedetomidine HCl use have been conducted in pediatric patients for sedation in the critical care units and for sedation in non-invasive procedures (i.e., radiology),[16,17,18,19] which may explain the capture of drug utilization data for dexmedetomidine use in pediatric patients.

Findings from this review should be interpreted in the context of the known limitations of the databases used. The IMS Hospital CDM sample does not include federal hospitals (e.g., VA facilities) and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Also not included are ambulatory facilities where procedures are performed using dexmedetomidine (e.g. 'free standing' medical imaging centers). Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS patient level data to be representative and accurate across multiple therapeutic areas.

Regarding the FAERS data, we do not consider the unlabeled events to be new safety signals because of related information in existing labeling and/or confounding factors. The labeled events are consistent with existing labeling.

Our FAERS review of pediatric patients who received DEX found 37 serious cases. More than half (22/37; 59%) were <6 years-old, and 13/37 (35%) were >1 month and ≤ 2 years-old. Two of the 37 cases were fatal, and although the cases were confounded by concurrent disease, DEX administration could have been a contributing factor in the deaths. We determined a key event for each case and subsequently a key event category. The most common event category was cardiovascular and the most common cardiac events were the labeled event cardiac arrest (n=4) and the unlabeled event syncope (n=3). The next most common event category was and neuropsychiatric (NPS). The most common NPS events were the labeled events of convulsion (n=4) and communication disorder (n=2) and the unlabeled event of encephalopathy (n=2).

When reported, more FAERS cases described patients ventilated in an ICU/OR setting (n=18) than non-ventilated for a procedure (n=6). Short-term (≤ 24 hours) and long-term (>24 hours; not indicated) infusions were about equally reported. Most of the infusion cases (21/35)[20] reported events that occurred during the DEX infusion. There were 14 cases that reported events after DEX infusion discontinuation; eight of these may have been related to DEX withdrawal.

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[16]Phan H, Nahata MC. Clinical uses of dexmedetomidine in pediatric patients. Paediatr Drugs. 2008;10(1):49-69.
[17]Chrysostomou C[1], Di Filippo S, Manrique AM, Schmitt CG, Orr RA, Casta A, Suchoza E, Janosky J, Davis PJ, Munoz R. Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med. 2006 Mar;7(2):126-31.
[18]Chrysostomou C, Sanchez De Toledo J, Avolio T, Motoa MV, Berry D, Morell VO, Orr R, Munoz R. Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants after cardiac surgery? Pediatr Crit Care Med. 2009 Nov;10(6):654-60. doi: 10.1097/PCC.0b013e3181a00b7a.
[19]Su F, Nicolson SC, Zuppa AF. A dose-response study of dexmedetomidine administered as the primary sedative in infants following open heart surgery. Pediatr Crit Care Med. 2013 Jun;14(5):499-507. doi: 10.1097/PCC.0b013e31828a8800.
[20]Excluding two cases with nasal (Section 3.4.1) and unintentional bolus (Section 3.4.5) administration.

There were 14 non-fatal FAERS cases that described events after DEX infusion discontinuation. DEX labeling mentions withdrawal as a *Warning* (Section 5.5) supported by clinical trial data and lists tachycardia, hypertension, nausea, vomiting, and agitation as clinical symptoms of withdrawal. Labeling also describes[21] that DEX, due to similar pharmacology can have a 'clonidine like withdrawal syndrome.' Eight of the 14 'post DEX infusion' cases appear to be withdrawal related. Half (n=4) of the cases described tachycardia (labeled).[22] The remaining four 'withdrawal' cases had neuropsychiatric (NPS) events (Section 3.4.2. of this review). Of these NPS events, only agitation is described in current labeling for withdrawal.[23] The other events (e.g., movement disorders, combativeness, mental status changes) are not currently labeled in the context of withdrawal; however these cases were also confounded by other factors. DEX labeling states that withdrawal was not seen after infusions less than 6 hours in adult subjects for procedural sedation. This is consistent with what we found in FAERS as all eight 'withdrawal' cases had long-term infusions.

5 CONCLUSION

Our drug use analysis found that pediatric patients accounted for approximately 13%-19% of total patients who had a hospital billing for dexmedetomidine HCl injection from June 2010 through May 2015. Patients aged 2-11 years old accounted for the largest proportion of DEX use among the pediatric patients captured. For the FAERS cases, more than half (22/37) were <6 years-old, and 13/37 cases were in patients >1 month and ≤ 2 years-old.

There is no evidence from these data that there are new pediatric safety concerns with DEX at this time.

6 RECOMMENDATION

We recommend routine pharmacovigilance monitoring for DEX.

[21]Precedex labeling: Section 9: Drug Abuse and Dependence; See Appendix A.
[22]The reporter (author: *Shiba* lit) claims that the 1 year-old's cardiac failure (*preceded by tachycardia*), all of which occurred post DEX discontinuation (Section 3.4.1, this review) was due to withdrawal. We acknowledge tachycardia as associated with withdrawal. The cardiac failure was confounded by the patient's medical history and we do not consider such to be a result of DEX withdrawal.
[23]Speech disorder is labeled but is not described in the setting of withdrawal (Appendix E).

Reference ID: 3899882

7 APPENDICES

7.1 APPENDIX A. PRECEDEX LABEL: WARNINGS, DRUG INTERACTIONS, AND DRUG ABUSE

Label Section	Title	Text
5.2	Hypotension, Bradycardia, and Sinus Arrest†	Reports of hypotension and bradycardia have been associated with Precedex infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Precedex, increasing the rate of intravenous fluid administration, elevation of the lower extremities, and use of pressor agents. Because Precedex has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of Precedex-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required. Caution should be exercised when administering Precedex to patients with advanced heart block and/or severe ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly
5.3	Transient Hypertension	Transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of Precedex. Treatment of the transient hypertension has generally not been necessary, although reduction of the loading infusion rate may be desirable.
5.4	Arousability	Some patients receiving Precedex have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.
5.5	Withdrawal Intensive Care Unit Sedation	With administration up to 7 days, regardless of dose, 12 (5%) Precedex adult subjects experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing study drug and 7 (3%) Precedex adult subjects experienced at least 1 event 24 to 48 hours after end of study drug. The most common events were nausea, vomiting, and agitation. In adult subjects, tachycardia and hypertension requiring intervention in the 48 hours following study drug discontinuation occurred at frequencies of <5%. If tachycardia and/or hypertension occurs after discontinuation of Precedex supportive therapy is indicated.
	Withdrawal Procedural Sedation	In adult subjects, withdrawal symptoms were not seen after discontinuation of short-term infusions of Precedex (<6 hours).
5.6	Tolerance and Tachyphylaxis	Use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions [see Adverse Reactions (6.1)].
5.7	Hepatic Impairment	Since Precedex clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function [*see Dosage and Administration (2.2)*].

Label Section	Title	Text
7.1	Drug Interactions: Anesthetics, Sedatives, Hypnotics, Opioids	Co-administration of Precedex with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between Precedex and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with Precedex, a reduction in dosage of Precedex or the concomitant anesthetic, sedative, hypnotic or opioid may be required.
9.3	Drug Abuse and Dependence: Dependence	The dependence potential of Precedex has not been studied in humans. However, since studies in rodents and primates have demonstrated that Precedex exhibits pharmacologic actions similar to those of clonidine, it is possible that Precedex may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation [*see Warnings and Precautions (5.5)*].
[†]This section is excerpted; all other sections are verbatim.		

7.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

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, eaches, 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.

IMS, Inpatient HealthCare Utilization System (IHCarUS)

IMS longitudinally tracks patient-level diagnoses, procedures, and drug utilization within hospitals (inpatients and outpatients). CDM is a collection of data streams that is large, well distributed, and geographically representative. IMS collects and maintains patient-level hospital inpatient and hospital outpatient (including all ED) setting data from more than 630 hospitals, covering each census region of the United States (US), including all inpatient hospital and outpatient (including ED) hospital patient level records. The hospital data is collected electronically on a weekly and monthly basis from hospital CDM patient level records. Data fields collected include diagnoses, procedures, drugs (i.e., ingredient name, brand name, strength, and daily administrations), and location of each service and room type (e.g. Pediatric ICU) by day of stay The hospital inpatient and outpatient patient records are linked longitudinally through unique patient-level IDs. The lag time between the hospital encounter date and availability of IMS' hospital inpatient and hospital outpatient raw and projected hospital data and reporting is 25-30 days.

All IMS data is third-party verified HIPAA-compliant with patients being assigned a unique anonymized patient ID, which allows IMS to track patients anonymously and longitudinally over time. IMS also has the ability to match their anonymized patient ID's and records to government and commercial patient registries utilizing anonymized patient IDs. IMS datasets are geographically representative and well characterized, providing a high degree of accuracy in projections to the US population.

7.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.4 APPENDIX D. FAERS CASE SERIES FOR DEXMEDETOMIDINE (N=37)

Case ID - Version #	Key event	Country	Mfr control # (or Direct report)	Reference (if literature report)
9391820- 1	Adrenal insufficiency	US	1790100	Tucker EW, et al. Dexmedetomidine infusion associated with transient adrenal insufficiency in a pediatric patient: a case report. Case Rep Pediatr. 2013; Art ID 207907; Published online 2013 May 16. doi: 10.1155/2013/207907
10673825- 1	Anaphylactic reaction	US	FK201406336	Nunziata R, et al. Intraoperative anaphylaxis: more common than we think. 68th Post-Graduate Assembly in Anesthesiology of the New York State Society of Anesthesiologists.
7418166- 2	Bradycardia	Foreign	602438	
10551376- 1	Bradycardia	Foreign	2595657	
4037194- 2	Bradycardia	US	B0312849A	Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. Pediatr Crit Care Med. 2003;4(2):203-205.
7414120- 1	Bradycardia	US	Direct report	
9478953- 1	Bradycardia	Foreign	1851877	Nath SS, Singh S, Pawar ST. Dexmedetomidine overdosage: an unusual presentation. Indian J Anaesth. 2013 May; 57(3): 289-291.
7845681- 1	Cardiac arrest	US	817047	Shepard SM, et al. Dexmedetomidine-related atrial standstill and loss of capture in a pediatric patient after congenital heart surgery. Crit Care Med. 2011;39(1):187-189.
8514160- 1	Cardiac arrest	Foreign	IN-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201201405	Bharati S, Pal A, Biwas C, Biwas R. Incidence of cardiac arrest increases with the indiscriminate use of dexmedetomidine: a case series and review of published case reports. Acta Anaesthesiol Taiwan. 2011;49:165-167.
6302758- 1	Cardiac arrest	US	Direct report	
10570161- 4	Cardiac failure	Foreign	2605767	Shiba J, et al. Acute heart failure due to dexmedetomidine withdrawal: a case report. Clinical Pediatric Anesthesia. 2014;20(1):169.
8911818- 1	Cardiac failure	US	1485297	Gupta, et al. Safety and efficacy of prolonged dexmedetomidine use in critically ill children with heart disease. Ped Crit Care Med. 2012;13:660-666.
7152646- 3	Cerebral infarction	Foreign	391630	Satou D and Harama R. The usability of dexmedetomidine during postoperative management after encephalo-duro-aterio-synangiosis with moyamoya disease. 15th Annual Meeting of the Japanese Society of Pediatric Anesthesiology. 97; I-05-04 Preoperative/Postoperative Management.
8548158- 1	Communication/ speech disorder	US	1268384	Miller JL, Johnson PN, Allen C. Neurologic withdrawal symptoms following abrupt discontinuation of a prolonged dexmedetomidine infusion in a child. J Pediatr Pharmacol Ther. 2010;15(1):38-42.
6686479- 1	Communication/ speech disorder	US	Direct report	
8718282- 2	Convulsion	Foreign	1344827	Kubota T, Fukasawa T, Kitamura E, et al. Epileptic seizures induced by dexmedetomidine in a neonate. Brain Dev. 2013;35:360-362.

Reference ID: 3899882

Case ID - Version #	Key event	Country	Mfr control # (or Direct report)	Reference (if literature report)
6443630- 1	Convulsion	Foreign	07H-008-0313260-00	
6443622- 1	Convulsion	Foreign	07H-008-0313259-00	
7635498- 7	Drug reaction with eosinophilia and systemic symptoms	Foreign	JP-PFIZER INC-2010098000	Shigematsu Y. A case of child DIHS due to phenobarbital presenting multiple drug sensitization. Japanese Journal Of Dermatology. 2011;121(3):574.
10392402- 1	Encephalopathy	US	2487340	Hoehn K, Pillai S, Brouillette G. Posterior reversible encephalopathy syndrome from dexmedetomidine discontinuation. Crit Care Med. 2013; 41(12):A289.
7953508- 1	Encephalopathy	US	Direct report	
8520610- 2	Hepatitis fulminant	Foreign	JP-BAYER-2012-037134	
6953412- 1	Hypoglycemia	US	213946	Bernard PA, Makin CE, Werner HA. Hypoglycemia associated with dexmedetomidine overdose in a child? J Clin Anesth. 2009;21:50-53.
6354197- 1	Hypothermia	US	07H-163-0312774-00	Finkel JC and Quezado ZM. Hypothermia-induced bradycardia in a neonate receiving dexmedetomidine. J Clin Anesth. 2007;19:290-292.
8011519- 1	Myoclonus	US	PHHY2011US55199	Belgrade M and Hall S. Dexmedetomidine infusion for the management of opioid-induced hyperalgesia. Pain Med. 2010;11(12):1819-1826.
9778760- 2	Psychosis	Foreign	IN-PURDUE-GBR-2013-0016588	Ahuja V, Goel N, Das S, Singh P. Intensive care unit psychosis a well-known fact but rarely thought early. J Anaesthesiol Clin Pharmacol. 2013;29:413-4.
7998254- 1	QT prolongation	Foreign	930717	Matras ME, Lavole A, Closon A, Bussieres JF. QT interval prolongation and polypharmacy in pediatrics. Quebec Pharmacie. 2011;58:45-49.
7614112- 1	Sedation	US	693593	Max BA and Mason KP. Extended infusion of dexmedetomidine to an infant at sixty times the intended rate. Internat J Peds. 2010; Article ID 825079. Pii: 825079. doi: 10.1155/2010/825079. Epub 2010 Sep 8.
6593806- 1	Supraventricular tachycardia	Foreign	DX3070067B	Yamamoto S, et al. Three cases of post pediatric heart operation tachycardia after dexmedetomidine discontinuation. Clin Ped Anesth. 2007;13(1):119.
8744494- 1	Syncope	US	Direct report	
10029841- 1	Syncope	US	2247258	Patel VJ, Ahmed SS, Nitu ME, Rigby MR. Vasovagal syncope and severe bradycardia following intranasal dexmedetomidine for pediatric procedural sedation. Pediatr Anesth. 2014 Feb 26:1-3.
8798167- 4	Syncope	US	US-JNJFOC-20120907543	
6593812- 1	Tachycardia	Foreign	DX3070067A	Yamamoto S, et al. Three cases of post pediatric heart operation tachycardia after dexmedetomidine discontinuation. Clin Ped Anesth. 2007;13(1):119.
10349452- 3	Tachycardia	Foreign	2456794	Higashi M, et al. A case of mitochondrial encephalomyopathy with sympathicotonia due to dexmedetomidine withdrawal. 22nd Tokai-Hokuriku Regional Meeting of the Japanese Society of Intensive Care Medicine. 23-Jul-2014.

Case ID - Version #	Key event	Country	Mfr control # (or Direct report)	Reference (if literature report)
6178578- 1	Torsades	Foreign	06H-129-0311113-00	
9254944- 1	Torsades	US	1678593	Burns KM, Greene EA. Long QT syndrome unmasked by dexmedetomidine: a case report. Congenit Heart Dis. 2014;9(1):E11-E15.
7105016- 1	Upper airway obstruction	US	357564	Lubisch N, et al. Dexmedetomidine for procedural sedation in children with autism and other behavior disorders. Pediatr Neurol. 2009;41:88-94.

7.5 Appendix E. Precedex Package Insert Location For Labeled Events From FAERS Non-Fatal Case Series (N=35)

		CARDIOVASCULAR					NEUROPSYCHIATRIC					OTHER	
SELECED SECTIONS FROM PRECEDEX LABELING		brady-cardia	cardiac arrest	QT prolong-ation	supra-ventric-ular tachy cardia	tachy-cardia	com-munica-tion/ speech disorder	convul-sion	myoclonus	psychosis	seda-tion	hypo-glycemia	upper airway obstruc-tion
Section #	Section Title												
1	**INDICATIONS AND USAGE**												
1.1	Intensive Care Unit Sedation										x		
1.2	Procedural Sedation										x		
5	**WARNINGS AND PRECAUTIONS**												
5.2	Hypotension, Bradycardia, and Sinus Arrest	x	as 'sinus' arrest										
5.5	Withdrawal					x							
5.6	Tolerance and Tachyphylaxis					x							
6	**ADVERSE REACTIONS**												
6.1	Clinical Studies Experience												
	Table 2: AEs: ICU Sedation <24 hrs; >2%	x				x							
	Table 3: AEs: ICU Sedation <24 hrs; >1`%	x				x							
	Table 4: AEs: Long-term ICU Sedation' DEX or MDZ	x				x						x	Footnote 1
	Table 5: Long-term ICU Sedation' DEX or MDZ: Maintenance dose related increase in AE s												Footnote 1

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		CARDIOVASCULAR					NEUROPSYCHIATRIC					OTHER	
		brady-cardia	cardiac arrest	QT prolong-ation	supraven-tricular tachy-cardia	tachy-cardia	com-munica-tion/ speech disorder	convul-sion	myoclonus	psychosis	seda-tion	hypo-glycemia	upper airway obstruc-tion
	Table 6: AEs, Procedural Sedation; >2%	x				x							as respira tory depres sion
6.2	Postmarketing Experience												
	Table 7: AEs Post Approval	x	x	X (HQ Specialty product)	x	x	speech disorder	x	as 'convulsion'	Footnote 3		x	Footnote 2
13	**NONCLINICAL TOXICOLOGY**												
13.2	Animal Pharmacology and/or Toxicology												
14	**CLINICAL STUDIES**												
14.1	Intensive Care Unit Sedation										x		
14.2	Procedural Sedation										x		
17	**PATIENT COUNSELING INFORMATION**										x		

Footnotes:	
1	as respiratory failure, acute respiratory distress syndrome
2	as apnea, dyspnea, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis
3	as confusional state, delirium, hallucination, illusion

Reference ID: 3899882

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/s/

MARTIN L POLLOCK
03/10/2016

JENNIE Z WONG
03/10/2016

SARA L CAMILLI
03/10/2016

RAJDEEP K GILL
03/10/2016
Drug use data has been cleared by datavendors.

GRACE CHAI
03/10/2016

STEVEN C JONES
03/10/2016