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## **EXECUTIVE SUMMARY**

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of desflurane in pediatric patients. Up to the "data lock" date of 10/13/2007, AERS contained 631 reports for desflurane (crude counts, listed as suspect or concomitant medication, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 7 % of the total (47/631).

DAEA 2 was asked to focus on the 1-year period following the approval of pediatric exclusivity, 09/13/2006 to 09/13/2007. We used an AERS data lock date of 10/13/2007, to allow time for reports received up to 09/13/2007, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 42 reports (crude counts, listed as suspect or concomitant medication, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 14% of the total number of cases (6/42). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review. Out of these six pediatric cases, 2 unduplicated cases were included in this case series. One case involved a fatal respiratory arrest and the other case involved prolonged coagulation time; the contributory role of desflurane could not be excluded in these cases.

Due to the limited number of pediatric cases during the pediatric exclusivity period, DAEA 2 was asked to conduct an additional search of AERS to identify all adverse events associated with desflurane use in pediatric patients from market approval to the pediatric exclusivity period (9/18/1992 to 09/13/2006). This search identified 31 cases of desflurane use where the contributory role of desflurane could not be excluded. Most of the cases involved labeled adverse events for desflurane; respiratory and cardiovascular disorders were the most reported adverse events. The unlabeled events included cardiac arrest, prolonged coagulation time, seizures, transient blindness, pulmonary edema, and muscle twitches; although these cases were strongly confounded with the use of concomitant medications labeled with these events, the contributory role of desflurane could not be ruled out.

Death was reported in three cases, one during and two prior to the pediatric exclusivity period, and involved events that are already labeled for desflurane. The reported causes of death in the three fatal cases (e.g. respiratory arrest, hypoxic brain damage, and rhabdomyolysis) could not be solely attributed to the use of desflurane. Concomitant medications were also likely to have contributed to the outcomes.

In total, the 33 pediatric cases that were included in this review did not reveal any notable unexpected safety concerns associated with desflurane use in pediatric patients. However, the safety review identified 3 cases of cardiac arrest, which is not specifically labeled for desflurane. Concomitant medications confounded the causality assessment of all cases throughout this review. We believe that the labeling should be revised to include cardiac arrest. DAEA 2 will continue routine monitoring of adverse events with the use of desflurane in pediatric patients.

## **1 BACKGROUND**

### **1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)**

Desflurane is a general inhalation anesthetic. It is a nonflammable liquid administered via vaporizer. Desflurane is a colorless, volatile liquid below 22.8°C. Desflurane is packaged in amber-colored bottles containing 240 mL.

Desflurane is indicated:

- *As an inhalation agent for induction and/or maintenance of anesthesia for inpatient and outpatient surgery in adults.*
- *For maintenance of anesthesia in infants and children after induction of anesthesia with agents other than desflurane, and tracheal intubation.*
- *Not recommended for induction of anesthesia in pediatric patients because of high incidence of moderate to severe upper airway adverse events.*

## **1.2 PEDIATRIC LABELING**

The labeling for pediatric use includes the following information<sup>1</sup>:

*Desflurane is approved for maintenance of anesthesia in infants and children after induction of anesthesia with agents other than desflurane, and tracheal intubation.*

*Desflurane is not recommended for induction of general anesthesia via mask in children because of the high incidence of moderate to severe respiratory adverse reactions, including laryngospasm (50%), coughing (72%), breathholding (68%), increase in secretions (21%) and oxyhemoglobin desaturation (SpO<sub>2</sub> <90%) (26%) seen in clinical studies.*

*Desflurane is not approved for maintenance of anesthesia in non-intubated children due to an increased incidence of respiratory adverse reactions.*

*In a clinical safety trial conducted in children aged 2 to 16 years (mean 7.4 years), following induction with another agent, desflurane and isoflurane (in N<sub>2</sub>O/O<sub>2</sub>) were compared when delivered via face mask or laryngeal mask airway (LMA) for maintenance of anesthesia, after induction with intravenous propofol or inhaled sevoflurane, in order to assess the relative incidence of respiratory adverse events.*

*Desflurane was associated with higher rates (compared with isoflurane) of coughing, laryngospasm and secretions with an overall rate of respiratory events of 39%. Of the pediatric patients exposed to desflurane, 5% experienced severe laryngospasm (associated with significant desaturation; i.e. SpO<sub>2</sub> of <90% for >15 seconds, or requiring succinylcholine), across all ages, 2-16 years old. Individual age group incidences of severe laryngospasm were 9% for 2-6 years old, 1% for 7-11 years old, and 1% for 12-16 years old. Removal of LMA under deep anesthesia (MAC range 0.6 – 2.3 with a mean of 1.12 MAC) was associated with a further increase in frequency of respiratory adverse events as compared to awake LMA removal or LMA removal under deep anesthesia with the comparator. The frequency and severity of non-respiratory adverse events were comparable between the two groups. The incidence of respiratory events under these conditions was highest in children aged 2-6 years. Therefore, similar studies in children under the age of 2 years were not initiated.*

## **2 METHODS AND MATERIALS**

### **2.1 INTRODUCTION**

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues.

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<sup>1</sup> Suprane (desflurane) product label, December 2006, Baxter

## 2.2 AERS SELECTION OF CASES

### 2.2.1 1-YEAR PEDIATRIC EXCLUSIVITY PERIOD (9/13/2006 TO 10/13/2007)

The AERS database retrieved 6 pediatric reports associated with desflurane that were received during the 1-year post-pediatric exclusivity period. Of the 6 cases, 2 unduplicated pediatric cases were included in this case series. The remaining 4 cases were excluded for the following reasons.

<b>Table 1: Reasons for exclusion and number of excluded AERS cases (n=4)</b>	
Duplicate reports	2
Adverse events unlikely related to desflurane	2
<b>Total</b>	<b>4</b>

### 2.2.2 MARKET APPROVAL TO PEDIATRIC EXCLUSIVITY PERIOD (9/18/1992 TO 9/13/2006)

The AERS database retrieved 41 reports associated with desflurane from market approval to the pediatric exclusivity period. Of the 41 cases, 31 unduplicated pediatric cases were included in this case series. The remaining 10 cases were excluded for the following reasons.

<b>Table 2: Reasons for exclusion and number excluded AERS cases (n=10)</b>	
Duplicate reports	1
Adult report miscoded as pediatric	1
Adverse event unlikely related to desflurane	8
<b>Total</b>	<b>10</b>

## 3 AERS RESULTS FOR *DESFLURANE*

### 3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY PERIOD (9/13/2006) TO 10/13/2007 (TABLE 3)

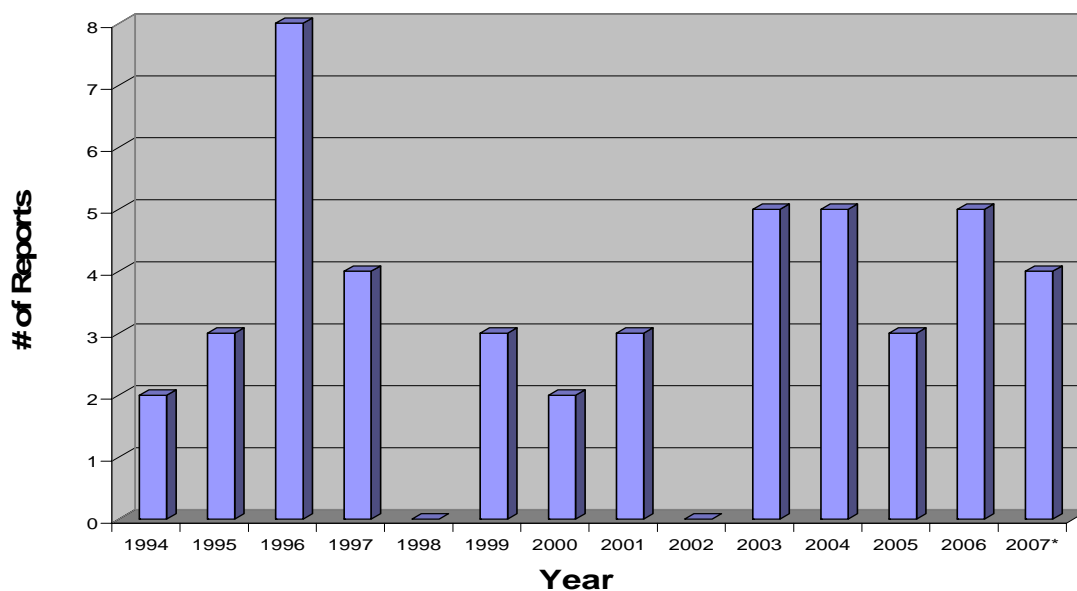
<b>Table 3: Crude counts<sup>1</sup> of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (9/13/2006) to 10/13/2007 (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	30 (5)	28 (3)	2 (1)
Pediatrics (0-16 yrs)	6 (1)	6 (1)	3* (0)
Age unknown (Null Values)	6 (1)	6 (1)	0 (0)
<b>Total</b>	<b>42 (7)</b>	<b>40 (5)</b>	<b>5 (1)</b>
* One unduplicated death case			
<sup>1</sup> May include duplicates			
<sup>2</sup> Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.			

### 3.2 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL (9/18/1992) TO 10/13/2007 (TABLE 4)

<b>Table 4: Crude counts<sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date (9/18/1992) to 10/13/2007 (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	488 (303)	392 (215)	81 (36)
Pediatrics (0-16 yrs.)	47 (26)	39 (21)	5* (1)
Age unknown (Null values)	96 (58)	42 (29)	2 (2)
Total	631 (387)	473 (265)	88 (39)

\* Three unduplicated death cases  
<sup>1</sup> May include duplicates  
<sup>2</sup> Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

**Figure 1: AERS Reporting trend for pediatric reports from approval date (9/18/1992) to 10/13/2007**



\* Includes reports up to 10/13/2007

### 3.3 CASE CHARACTERISTICS FROM PEDIATRIC EXCLUSIVITY PERIOD (TABLE 5)

Table 5 below describes the characteristics of the 2 pediatric cases reported during the one-year pediatric exclusivity period.

<b>Table 5 : Characteristics of AERS pediatric cases reported during the pediatric exclusivity period (09/13/2006) to 10/13/2007 n=2</b>	
Gender [n=2]	Female: (2)
Age [n=2]	5 months and 2 years
Indication [n=2]	Anesthesia (2)
Event [n=2]	Respiratory arrest (1), Coagulation time prolonged (1)

<b>Table 5 : Characteristics of AERS pediatric cases reported during the pediatric exclusivity period (09/13/2006) to 10/13/2007 n=2</b>	
Time to onset of event [n=2]	7 and 8 hours
Outcomes [n=2]	Death: (1), Life-Threatening: (1)
Positive Rechallenge / Dechallenge	None (Events occurred after desflurane was discontinued in both cases)
FDA received date [n=2]	2006: (1), 2007: (1)
Source [n=2]	Foreign: (2)
Type of report [n=2]	15-day (2)
Reporter [n=2]	Healthcare professional (2)

### **3.4 CASE CHARACTERISTICS FROM MARKET APPROVAL TO PEDIATRIC EXCLUSIVITY PERIOD (TABLE 6)**

Table 6 below describes the characteristics of the 31 pediatric cases reported from market approval date to the pediatric exclusivity period.

<b>Table 6 : Characteristics of pediatric cases reported from market approval date (9/18/1992) through 9/13/2006 n=31</b>	
Gender [n=31]	Male: (20) Female: (11)
Age [n=31]	0- <1 month: (1) 1 month <2 yrs: (3) 2-5 yrs: (3) 6-11 yrs: (8) 12-16 yrs: (16) Mean (10 yrs)
Indication [n=31]	Anesthesia (31)
Drug strength [n=11]	Range (1-12.4%) median (7.8%)
Event [n=31]	Hypoxia (1), rhabdomyolysis (1), malignant hyperthermia (3), cardiac arrest (3), arrhythmia (2), laryngospasm (2), bronchospasm (3), pulmonary edema (1), apnea (2), seizure(2), transaminitis (3), hypertension (3), hypotension (1), vomiting(2), hyperkalemia (1), muscle twitch (1)
Time to onset of event [n=30]	Range (1 minute to 7 days) median (10 minutes)
Outcomes [n=31]	Death: (2), Life-Threatening: (11), Hospitalization: (6), Other: (8), Requiring intervention: (1), Not reported (3)
Rechallenge [n=1]	Positive rechallenge (1)
FDA received date [n=31]	1994 (2), 1995 (1), 1996 (8), 1997 (3), 1999(1), 2000 (2), 2001 (3), 2003 (2), 2004 (5), 2005 (3), 2006 (1)
Source [n=31]	US: (20) Foreign: (11)
Type of report [n=31]	15 day (17), Direct (5), Periodic (9)
Reporter [n=31]	Physician (18), Pharmacist (6), Other healthcare professional (7)

## **4 DISCUSSION OF CASES FROM PEDIATRIC EXCLUSIVITY PERIOD**

The two cases received during the pediatric exclusivity period were both foreign cases. The patients were female and their ages were 5 months and 2 years. The reported events were respiratory arrest and prolonged coagulation time. Time to event was similar in both cases, 7 and 8 hours, respectively. Serious outcomes included death in one case and life-threatening events in the other case. Both cases were included in this case series because the contributory role of desflurane could not be excluded. These 2 cases are discussed in more depth below:

#### **4.1 FATAL CASE (N= 1)**

##### **Respiratory Arrest**

One case of death was identified during the one-year pediatric exclusivity period. In this case, a five month old female was administered propofol, atracurium besylate, and desflurane, as general anesthesia for incision and drainage of a left thigh abscess at the site of a third DTP/polio immunization. Propofol, atracurium besylate, and desflurane are all labeled for severe respiratory adverse events, including respiratory depression. Seven hours after completion of uncomplicated general anesthesia, the patient experienced an unexplained respiratory arrest. The patient was resuscitated, but died six days later in the pediatric ICU. An autopsy was performed which reported the cause of death as respiratory arrest. Histology revealed that the patient's diaphragm was abnormal with very unusual necrotizing myopathy of the diaphragm. The reporter thought that the unusual necrotizing myopathy of the diaphragm explained the patient's respiratory arrest. However, the cause of the necrotizing myopathy of the diaphragm was unclear. Idiosyncratic drug reaction was another suggested possibility, by the reporter, for the events of this case.

*Propofol, atracurium besylate, and desflurane are all labeled for severe respiratory adverse events, including respiratory depression. The patient's diaphragm abnormalities and the concomitant use of propofol and atracurium besylate provided plausible explanations for the patient's respiratory arrest and death. This case was included because desflurane is labeled for severe respiratory adverse events and the contributory role of desflurane could not be excluded.*

#### **4.2 NON-FATAL CASE (N=1)**

##### **Coagulation Time Prolonged**

A two year old female with an artificial mitral valve developed prolonged coagulation time and bleeding, following an unknown surgical procedure. She had an INR of 3.7 two days prior to surgery and was taking acenocoumarol. During surgery, she was given propofol, midazolam, ketamine, sevoflurane, and desflurane for anesthesia. The patient's INR increased to 9, with bleeding, eight hours after surgery. Corrective treatment was not reported. The patient recovered without sequelae. The French Medicine Agency suspected an interaction between acenocoumarol and any one of the following drugs: propofol, acetaminophen, midazolam, ketamine, sevoflurane, and desflurane.

*There is a lack of data on possible pharmacokinetic interactions between desflurane and acenocoumarol. However, desflurane, at least based upon experimental animal studies, has the ability to interact with the drug eliminating capacity of the liver.<sup>2</sup> The association between prolonged coagulation time and desflurane appears questionable, but the contributory role of desflurane could not be excluded given the potential interaction. In this case, according to the reporter, desflurane may have interacted with the patient's liver metabolism and decreased the patient's clearance of acenocoumarol, resulting in an elevated INR and bleeding.*

## **5 DISCUSSION OF CASES PRIOR TO 1-YEAR PEDIATRIC EXCLUSIVITY PERIOD**

Since only 2 pediatric cases were identified during the 1-year post pediatric exclusivity period, an additional request was made by OPT to review all pediatric adverse events that were received between drug marketing and the start of the pediatric exclusivity period. Thirty-one pediatric

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<sup>2</sup> Dale O. 8 Drug interactions in anesthesia: focus on desflurane and sevoflurane. *Baillière's Clinical Anesthesiology*. 1995; 9:105-117.

cases were identified during this period. The majority (65%) of the reports were domestic cases. The age of the patients ranged from 1 month to 16 years with the mean of 10 years. Regarding gender, the majority (65%) of reports involved male patients. The reported events were: hypoxia (1), rhabdomyolysis (1), malignant hyperthermia (3), cardiac arrest (3), arrhythmia (2), laryngospasm (2), bronchospasm (3), pulmonary edema (1), apnea (2), seizure(2), transaminitis (3), hypertension (3), hypotension (1), vomiting(2), hyperkalemia (1), muscle twitch (1). Time to onset of events ranged from 1 minute to 7 days but in most cases (65%), the reported events occurred within 1 hour of receiving desflurane. The use of other concomitant medications was reported in 31 cases. Outcomes were death (2), life-threatening (11), hospitalization (6), requiring intervention (1), other (8), and not reported (3). These 31 cases are discussed in more detail below.

## **5.1 FATAL CASES (N=2)**

### **Respiratory Disorder**

**Hypoxia** was reported in one case, where the contributory role of desflurane could not be excluded. Hypoxia is labeled in the warnings section of the desflurane label. In this case, during leg surgery for an unreported condition, a nine year old female was given methohexital and isoflurane, which was switched to desflurane midway through surgery. The patient became severely hypoxic and bradycardic while receiving desflurane. Lungs revealed rales and pink frothy liquid was seen in the endotracheal tube. Vitals returned to normal after furosemide was given, but the patient failed to awaken from anesthesia. The patient died six days later from hypoxic brain damage. Her past medical history included anemia as a child. Desflurane and isoflurane were listed as the suspect medications. The doses of these medications were not reported.

*Respiratory depression, hypoxia, and bradycardia are labeled events for desflurane, isoflurane, and methohexital. Based on the plausible temporal relationship, it is possible that the adverse events were associated with any or all of the administered medications. It is not possible to determine which medication was more likely to be associated with the outcome since the medications were given closely together, and they are all labeled for the adverse events.*

### **Rhabdomyolysis**

**Rhabdomyolysis** was reported in one case, where the contributory role of desflurane could not be excluded. In this case, a five year old female patient received desflurane for general anesthesia during surgery for a meningomyelocele. Concomitant medications included propofol, dopamine, and piritramide. Three days after the surgery, the patient developed rhabdomyolysis. A diagnosis of renal failure and myocardial damage was made. The patient's creatine kinase reached 200,000. The patient died 18 days after surgery. The cause of death was not reported and an autopsy was not performed. The reporting physician stated that desflurane was not related to the events, but propofol was suspected to be related. Rhabdomyolysis is labeled in the warning section of the propofol labeling.

*Elevations in serum creatine kinase levels and changes in urine consistent with myoglobinuria are labeled events for desflurane. Therefore, the contributory role of desflurane in association with this case could not be excluded.*

## **5.2 NON-FATAL CASES (N=29)**

The remaining 29 non-fatal cases are discussed below in more detail. The reported events were:

- Malignant hyperthermia – 3

- Cardiac disorders – (cardiac arrest, arrhythmia) – 5
- Respiratory disorders – (laryngospasm, bronchospasm, pulmonary edema, apnea) – 8
- Nervous system disorders – (seizure) – 2
- Hepatic disorders – (transaminitis) – 3
- Vascular disorders – (hypertension, hypotension) – 4
- Gastrointestinal disorders – (vomiting) – 2
- Electrolyte imbalances – (hyperkalemia) – 1
- Muscle disorders – (twitch) – 1

### **Malignant hyperthermia (n=3)**

**Malignant hyperthermia** was reported in three cases, where the contributory role of desflurane could not be excluded. Malignant hyperthermia is labeled in the warnings section of the desflurane label. In all three reports, the patients were male and the patients all recovered after treatment with dantrolene. In the first case (13 yo M), malignant hyperthermia, acidosis, and hyperkalemia developed 90 minutes after desflurane was administered as an anesthetic for angiography. The patient had a family history of malignant hyperthermia thus increasing the patient's likelihood of developing malignant hyperthermia. Concomitant medications included fentanyl and propofol which both contain labeling for fever. In the second case (5 yo M), the patient developed malignant hyperthermia (39°C), masseter muscle spasm and rigidity, hypercapnia, and tachycardia after 15 minute infusion of desflurane during surgery for elective ear, nose, and throat surgery. Anesthetics were discontinued and the surgery was postponed. Concomitant medications included halothane and succinylcholine, both are labeled for malignant hyperthermia. Because desflurane was simultaneously used with concomitant medications also labeled for malignant hyperthermia, it is difficult to determine causality in this case. In the third case (10 yo M), the patient underwent surgery for fractures of the mandible and tibia and developed malignant hyperthermia (38.4°C), acidosis, and hypercapnia 10 minutes after desflurane was administered. The patient had no family history of malignant hyperthermia. Concomitant medications included succinylcholine, which is also labeled for malignant hyperthermia. This case of malignant hyperthermia is possibly associated with desflurane use.

*In all three cases, it is possible that malignant hyperthermia was associated with desflurane based on temporal association and the fact that desflurane is labeled for this event. However, family history of malignant hyperthermia and concomitant medications, also labeled for malignant hyperthermia, confounded the causality assessments of the three cases.*

### **Cardiac disorders - [cardiac arrest (n=3), cardiac arrhythmia (n=2)]**

**Cardiac arrest** was reported in three cases, where the contributory role of desflurane could not be excluded. Cardiovascular adverse events, including the warning that desflurane be administered only by skilled personnel with immediately available access to circulatory resuscitation, are described in the warning section of the desflurane label; however, cardiac arrest is not specifically labeled. In the first case (3 yo M), cardiac arrest occurred while receiving desflurane during an elective surgical insertion of grommets into the patient's ears. Desflurane was increased from 8% to 12% during the procedure. The patient then developed laryngospasms, bradycardia, and cardiac arrest. The patient was quickly resuscitated, recovered, and was discharged the following day. The reporting physician did not provide his assessment regarding a possible association between the event and the use of desflurane; rather, he stated that, "these things happen". Concomitant medications included propofol and fentanyl, which both contain labeling for cardiac arrest. In the second case (14 month F), cardiac arrest occurred while

receiving anesthesia, including desflurane, during surgery for a supracondylar elbow fracture. The patient's oxygen saturation decreased and the patient had a brief 10-second cardiac arrest. The patient was given atropine and was able to be ventilated. The patient recovered and was discharged four days after the event. Concomitant medications included rapacuronium, lidocaine, propofol and sevoflurane, which all contain labeling for cardiac events. The simultaneous use of these medications during anesthesia confounded the causality assessment of this case. It is possible that desflurane is associated with this case; however, the concomitant medications may have also played a role in the event. In the third case (16 yo M), cardiac arrest occurred while receiving desflurane during surgery for scoliosis correction. After four hours of uneventful anesthesia with desflurane, normal sinus rhythm turned into ventricular tachycardia and then into ventricular fibrillation and cardiac arrest. The patient was given two 1mg epinephrine treatments and normal sinus rhythm was restored. The patient recovered and was discharged 10 days later. Past medical history included Duchenne muscular dystrophy, scoliosis, cardiomyopathy, COPD, and GERD. Concomitant medications included alfentanil, propofol, and rocuronium, which all containing labeling for cardiac events. In this case, the reporting physician attributed the cardiac arrest to desflurane and the patient's cardiomyopathy. As listed in the warning section of the desflurane label, patients with Duchenne muscular dystrophy are most vulnerable for developing cardiac arrhythmias, hyperkalemia, and death if given desflurane.

*Cardiac arrest is not a labeled event for desflurane. In all three cases, it is possible that the cardiac events were associated with desflurane based on temporal association and the fact that desflurane is labeled for cardiac events including myocardial infarct, arrhythmia, and unstable blood pressure. However, the simultaneous use of concomitant medications during anesthesia confounded the causality assessment of these cases.*

**Cardiac arrhythmias** were reported in two cases, where the contributory role of desflurane could not be excluded. Cardiac arrhythmias are labeled for desflurane. In the first case (12 yo M), the patient developed arrhythmia, tachycardia, hypotension, and shock while receiving desflurane during a heminephrectomy. These events occurred after 10 minutes of anesthesia. Anesthesia was conducted with desflurane 8-10%, propofol, vecuronium, and alfentanil. Propofol and alfentanil both contain labeling for arrhythmias. The physician switched to a different unspecified inhalation gas for anesthesia and the patient recovered completely. It is likely that the cardiac arrhythmia was associated with desflurane use since the events improved with dechallenge of desflurane and a switch to a different unspecified inhalation gas. In the second case (14 yo M), the patient developed tachycardia, tachyarrhythmia, and a rash while receiving desflurane during surgery for a ruptured appendix. Concomitant medications included rocuronium, fentanyl, midazolam, and thiopental. The patient remained on desflurane throughout the procedure and recovered completely. The patient recovered after receiving atropine and edrophonium, for the reversal of the neuromuscular blocking agent rocuronium. Rocuronium is labeled for arrhythmias and is the likely contributory medication based on positive dechallenge; however, the contributory role of desflurane could not be excluded due to a reasonable temporal relationship and the fact that cardiac arrhythmias are labeled for desflurane.

*In the two cases of cardiac arrhythmias it is possible that desflurane was associated with the adverse events. Simultaneous use of concomitant medications confounded the causality assessment of these cases. Cardiac arrhythmias are a labeled event for desflurane.*

**Respiratory disorders - [laryngospasm (n=2), bronchospasm (n=3), pulmonary edema (n=1), apnea (n=2)]**

According to the desflurane package insert, the incidences of respiratory events in adult and intubated pediatric patients are labeled as 3 % - 10% for laryngospasm, apnea, and increased cough.

**Laryngospasm** was reported in two cases, where the contributory role of desflurane could not be excluded. Laryngospasm is labeled for desflurane. In the first case (22 month F), the patient experienced laryngospasm after receiving desflurane for anesthesia during surgery for the insertion of a pin into her elbow. Anesthesia was maintained with 9-10% desflurane. Concomitant medications included halothane and fentanyl, which both contain labeling for laryngospasm. At the end of the procedure, the patient experienced laryngospasm with three reoccurrences, without secretions. The reporter could not rule out the role of desflurane in the event but suggested that a restrictive airway may have led to the onset of laryngospasm. The origin of the patient's restrictive airway was not reported in the case. In the second case (16 yo F), the patient experienced laryngospasm and extrapyramidal symptoms shortly after receiving desflurane for an unknown surgical procedure. Concomitant medications included ondansetron, propofol, fentanyl, and midazolam, which all contain labeling for laryngospasm. Propofol and fentanyl contain labeling for rigidity, while ondansetron contains labeling for dystonic reactions, which may have all contributed to the patient's extrapyramidal symptoms. The events persisted and required hospitalization. The patient's past medical history was unremarkable and MRI and chest X-ray were normal. The events resolved within five days. The reporting pharmacist considered the events were possibly related to ondansetron and propofol. This case was included since desflurane is labeled for laryngospasm, and it was possible that desflurane could have contributed to the development of laryngospasm.

*In the two cases of laryngospasm it is possible that desflurane was associated with the adverse event. However, simultaneous use of concomitant medications confounded the causality assessment of the two cases.*

**Bronchospasm** was reported in three cases, where the contributory role of desflurane could not be excluded. Bronchospasm is labeled for desflurane. In the first case (13 yo M), the patient experienced bronchospasm while receiving desflurane during a surgical operation for urethroplasty. All medications were discontinued and the patient fully recovered. Concomitant medications included propofol and sufentanil citrate, which both contain labeling for bronchospasms. In the second case (8 yo M), the patient experienced bronchospasm 3 minutes post-intubation with rapacuronium, desflurane, nitrous oxide, morphine, and thiopental. Albuterol was given for treatment of the bronchospasm and the patient's breath sounds cleared. In the third case (7 yo F), the patient experienced bronchospasm immediately after receiving rapacuronium, desflurane, and thiopental for intubation and anesthesia for repair of a vaginal laceration. The patient received albuterol and the patient's oxygen saturation remained at 90%.

*The three bronchospasm cases were included since a plausible time relationship existed between desflurane use and the event. Bronchospasm is labeled for desflurane and it is possible that desflurane was associated with the adverse event. However, simultaneous use of concomitant medications confounded the causality assessment of the three cases.*

**Apnea** was reported in two cases with desflurane use, where the contributory role of desflurane could not be excluded. Apnea is a labeled event for desflurane. In the first case (14 yo F), the patient became apneic while receiving desflurane for an unreported surgical procedure. Concomitant medications included fentanyl, bupivacaine, and lidocaine with epinephrine, which all contain labeling for apnea. In the second case (14 yo F), the patient had fixed dilated pupils and apnea requiring ventilator support following general anesthesia with desflurane for an elective major orthopedic surgery. Spontaneous respirations returned and the patient was discharged five days later with no signs of respiratory or neurological deficit. Concomitant medications included bupivacaine, lidocaine, and fentanyl, which all contain labeling for apnea. Past medical history was not reported in these 2 cases.

*The two cases of apnea were included because the role of desflurane could not be excluded. It is possible that desflurane was associated with apnea in these cases, but the simultaneous use of concomitant medications confounded the causality assessment.*

**Pulmonary edema** was reported in one case with desflurane use, where the contributory role of desflurane could not be excluded. Pulmonary edema is not labeled for desflurane. An eight year old male was given desflurane and remifentanyl for anesthesia during oral surgery. The patient emerged from anesthesia rapidly and developed pulmonary edema after biting on his airway tubing which caused fluids to collect in the patient's lungs. The patient recovered completely. The patient's medical history included being overweight and anemic.

*The patient's biting on his airway tubing appears to have caused pulmonary edema by enabling fluids to collect in the patient's lungs. The patient's rapid emergence from anesthesia may have indicated that an inadequate strength of desflurane was used which may have contributed to the biting of the airway tubing and to pulmonary edema. The strength of desflurane given to the patient was not reported.*

### **Central nervous disorders (n=2)**

**Seizures** were reported in two cases, where the contributory role of desflurane could not be excluded. Seizures are not labeled for desflurane. In the first case (1 month M), the patient developed general seizures at the conclusion of a surgical procedure to correct pyloric stenosis. Anesthesia was discontinued at the time of the seizures. The patient recovered completely. Past medical history included pyloric stenosis and congenital heart disease. Concomitant medications included midazolam, succinylcholine, and thiopental. Midazolam contains a boxed warning for seizures in neonates. In the second case (16 yo M), the patient developed "tonic-clonic like events" and experienced "blindness for a short time" after receiving a test dose of methohexital while undergoing arthroscopy. Concomitant medications included desflurane, fentanyl, and alfentanil. Methohexital contains labeling for seizures while fentanyl and alfentanil contain labeling for blurred vision. Seizure and transient blindness lasted for 60 -90 minutes after emergence from anesthesia. The patient recovered and had no recollection of the events. Patient's medical history was not reported.

*In the first case, midazolam was used which contains a boxed warning for seizures in neonates, and the seizure occurred after desflurane was discontinued. In the second case, the seizure occurred after a test dose of methohexital. Methohexital is labeled for seizures and provided a plausible explanation for the events; however, desflurane was given closely to the onset of the seizure. The simultaneous use of concomitant medications confounded the causality assessment of the two cases.*

### **Hepatic disorders (n=3)**

**Transaminitis** was reported in three cases, where the contributory role of desflurane could not be excluded. Hepatic failure and hepatic necrosis are labeled in the adverse reactions section of the desflurane labeling. In the first case (12 yo F), the patient developed upper quadrant tenderness and pruritus seven days after receiving desflurane during an uneventful outpatient laparoscopic cholecystectomy. Total anesthesia time was 50 minutes and included desflurane, nitrous oxide, fentanyl, and propofol. Propofol contains labeling for abnormal liver function. The patient presented to the emergency room seven days later with increased liver enzymes (AST 1,005). Viral testing for hepatitis was negative. The patient had liver enzymes drawn three days later with improved results (AST 67, ALT 284). This patient had no previous surgical history and no prior use of inhalational anesthetics. No other information regarding this patient's past medical history was provided in the report. In the second case (10 yo M), the patient underwent a closed reduction of a fractured arm under general anesthesia with desflurane, nitrous oxide, propofol,

and sufentanil. Propofol contains labeling for abnormal liver function. Total anesthesia time was 30 minutes. One week after the operation, the patient complained of nausea and vomiting. Serology was obtained for mononucleosis, CMV, and hepatitis, which were all negative. A liver function test was conducted 20 days after the operation, and was elevated (AST 599, ALT 1256). The patient recovered and the liver function tests conducted 42 days after the operation were normal (AST 33, ALT 33). The patient had no history of hepatitis and no past surgical procedures. In the third case (13 yo M), the patient received desflurane for anesthesia for a surgical treatment of a tibia fracture. Three days after the surgery, the patient experienced fever (40°C) and increased liver enzymes (AST 189, ALT 99). The patient was hospitalized and it was reported that his symptoms slowly improved three days after admission. Concomitant medications were acetaminophen and enoxaparin, which both contain labeling for hepatic disorders.

*It is possible that desflurane could have contributed to the liver disorder reported in the 3 cases. Baseline LFTs were not reported in any of the cases and medical histories did not include any reports of past hepatic disorders or alcohol use. Hepatic disorders are known adverse events for desflurane. However, simultaneous use of concomitant medications confounded the causality assessment of these three cases.*

#### **Vascular disorders - [hypertension (n=3), hypotension (n=1)]**

**Hypertension** was reported in three cases, where the role of desflurane could not be excluded. Desflurane is labeled for hypertension, and it is possible that desflurane could have contributed to the adverse events. In the first case (16 yo M), the patient underwent a bilateral ureteral procedure. The patient received rocuronium, thiopental, desflurane, and fentanyl during the operation. Pre-operative blood pressure was 131/78. Ten minutes after completion of surgery, the patient's blood pressure increased to 170/105 with a heart rate of 130 bpm. Blood pressure decreased over the next hour and was last reported to be 153/69 with a heart rate of 107 bpm. The concomitant medications (e.g., rocuronium, thiopental and fentanyl), all contain labeling for hypertension. In the second case (16 yo M), the patient underwent ureteral reimplantation while receiving rocuronium, desflurane, fentanyl, and thiopental for anesthesia, which all contain labeling for hypertension. After surgery, the patient became hypertensive and tachycardic during admission to the PACU. Hypertension resolved and the patient was transferred to the ward. In the third case (15 yo F), the patient received propofol, alfentanil, and desflurane, which all contain labeling for hypertension, during tonsillectomy. The patient developed hypertension and tachycardia 30 minutes after induction and received labetalol for the adverse events. The patient recovered and had no history of hypertension. In all three cases, the patient's hypertension improved after desflurane was discontinued.

*The role of desflurane could not be excluded in the three cases, and it is possible that desflurane might have contributed to the patient's hypertension. Simultaneous use of concomitant medications confounded the causality assessment of these cases. The cases did not report a past medical history of hypertension.*

**Hypotension** was reported in one case, where the role of desflurane could not be excluded. Desflurane is labeled for hypotension. In this case, a 13 year old male underwent an upper endoscopy and flex sigmoidoscopy while receiving 2% desflurane, propofol, lidocaine, and mivacurium. The patient became hypotensive and bradycardic (BP = 42/22, HR = 41 bpm) seven minutes after the patient received 2% desflurane. Desflurane was discontinued. The physician rechallenged the patient with 1% desflurane and again the patient became hypotensive (BP = 62/28). The procedure was stopped. Patient's past medical history included aortic arch dilation and von Willebrand disease. Past medical history did not include hypotension. Concomitant

medications included propofol, lidocaine, and mivacurium, which all contain labeling for hypotension.

*The contributory role of desflurane is probable in this case since hypotension reoccurred with desflurane on rechallenge. Desflurane is labeled for hypotension.*

### **Gastrointestinal disorders (n=2)**

**Vomiting** was reported in two cases, where the role of desflurane could not be excluded. Vomiting is a labeled event for desflurane. In the first case (11 yo M), the patient experienced prolonged vomiting and nausea after receiving desflurane for a left inguinal hernia repair. The events occurred three hours after surgery and resulted in prolongation of the patient's hospitalization. Concomitant medications included bupivacaine and morphine, which both contain labeling for vomiting. In the second case (13 yo M), the patient experienced six episodes of vomiting after receiving desflurane for a left tympanoplasty. The vomiting began twenty minutes after surgery and prolonged the patient's hospitalization. Concomitant medications included fentanyl and lidocaine with epinephrine, which both contain labeling for vomiting.

*Desflurane is likely to be associated with the adverse events in both cases since desflurane is labeled for vomiting. Simultaneous use of concomitant medications confounded the causality assessment of these cases.*

### **Electrolyte imbalances (n=1)**

**Hyperkalemia** was reported in 1 case, where the role of desflurane could not be excluded. Hyperkalemia is a labeled event in the warnings section of the desflurane labeling. In this case, a 14 year old male had a severe headache, nausea and vomiting. CT scan showed a large subarachnoid hemorrhage. The patient was scheduled for cerebral angiography and coil embolization of the aneurysm and developed hyperkalemia ( $K^+ = 7.6$ ) 45 minutes after induction of anesthesia. General anesthesia included propofol, lidocaine, fentanyl, rocuronium, and desflurane. Propofol contains labeling for hyperkalemia. No significant EKG or vital sign changes were noticed as a result of the patient's hyperkalemia. Anesthesia was discontinued. Two and four hours later, the patient's potassium level had decreased to 5.9 and 3.1 mmol/L, respectively. Treatment for the hyperkalemia included hyperventilation, sodium bicarbonate, and calcium chloride. The reporting physician stated the patient had normal preoperative and postoperative potassium levels. The patient developed hyperkalemia intraoperatively without known cause. The patient recovered and was discharged four days after the surgical procedure. Past medical history included no allergies, no medications, and no history of hyperkalemia.

*The details of this case support a possible relationship between desflurane use and hyperkalemia; however, the simultaneous use of concomitant medications confounded the causality assessment of this case. Hyperkalemia is a labeled event in the warnings section of the desflurane labeling.*

### **Muscle disorders (n=1)**

A **muscle twitch** was reported in one case, where the role of desflurane could not be excluded. Desflurane is not labeled for muscle twitches. An 11 year old female underwent tonsillectomy and adenoidectomy. Anesthesia included rocuronium, fentanyl, propofol, morphine, succinylcholine, and desflurane. After surgery, the patient experienced a twitch. The patient was treated with edrophonium, atropine, neostigmine, and glycopyrrolate. The patient recovered but was weak when she was extubated.

*Weakness and muscle twitches are labeled events in the rocuronium labeling. The reversal of the neuromuscular blockade using edrophonium, atropine neostigmine, and glycopyrrolate likely resulted in the development of a twitch. In this case, rocuronium probably contributed to the*

*development of a muscle twitch and weakness. The contributory role of desflurane could not be excluded given the temporal association.*

## **6 CONCLUSION**

In conclusion, the 33 pediatric cases that were included in this review did not reveal any notable unexpected safety concerns associated with desflurane use in pediatric patients. However, the safety review identified 3 cases of cardiac arrest, which is not specifically labeled for desflurane. Concomitant medications confounded the causality assessment of all cases throughout this review. Death was reported in three cases, one during and two prior to the pediatric exclusivity period, and involved events that are already labeled for desflurane. The reported causes of death in the three fatal cases (e.g. respiratory arrest, hypoxic brain damage, and rhabdomyolysis) could not be solely attributed to the use of desflurane. Concomitant medications were also likely to have contributed to the outcomes.

## **7 RECOMMENDATIONS**

We believe that the labeling should be revised to include cardiac arrest. DAEA 2 will continue routine monitoring of adverse events with the use of desflurane in pediatric patients.

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Concur:

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## APPENDICES

### Appendix I. Line listing of AERS pediatric desflurane cases (N=33)

ISRNUM	AGE	SEX	Country	Outcome	Drug Strength (Conc %)	EVENT	Concomitant medications (S) = suspect medications
<b>Fatal case during 1 year pediatric exclusivity period (09/13/2006 to 10/13/2007) (n=1)</b>							
5134735	5 mon	Female	GB	DE	NA	Respiratory arrest	Propofol (S), atracurium besylate (S), augmentin
<b>Non-fatal case during 1 year pediatric exclusivity period (09/13/2006 to 10/13/2007) (n=1)</b>							
5280626	2 yr	Female	FR	LT	NA	Coagulation time prolonged	Propofol (S), midazolam, sevoflurane, morphine, ketamine, paracetamol, acenocoumarol
<b>Fatal cases from market approval to pediatric exclusivity period (09/18/1992 to 09/13/2006) (n=2)</b>							
3663625	5 yr	Female	DE	DE	4%	Rhabdomyolysis	Propofol (S) Dopamine, piritamid
1823358	9 yr	Female	US	DE	NA	Respiratory disorder	Isoflurane (S), brevitol,
<b>Non-fatal cases from market approval to pediatric exclusivity period (09/18/1992 to 09/13/2006) (n=29)</b>							
1503466	16 yr	Male	US	OT	NA	Vascular -Hypertension	Zemuron (S), pentothal, fentanyl
1533194	22 mon	Female	US	NR	9-10%	Respiratory - Laryngospasm	Halothane, nitrous oxide, fentanyl
1656370	16 yr	Male	US	OT	NA	Vascular - Hypertension	Zemuron (S) fentanyl, pentothal
1664142	3 yr	Male	GB	LT	8-12 %	Cardiac – Cardiac arrest	Propofol, fentanyl
1748143	1 mon	Male	FR	HO	7.80%	CNS – Seizures	Thiopental, midazolam, succinylcholine, thiopentone

<b>ISRNUM</b>	<b>AGE</b>	<b>SEX</b>	<b>Country</b>	<b>Outcome</b>	<b>Potency (Conc %)</b>	<b>EVENT</b>	<b>Concomitant medications (S) = suspect medications</b>
1767520	10 yr	Male	US	LT	6%	Malignant hyperthermia	Succinylcholine (S), thiopentone, fentanyl,
1810380	5 yr	Male	US	LT	NA	Malignant hyperthermia	Halothane (S), succinylcholine (S), atropine, nitrous oxide
1811756	16 yr	Male	US	NR	NA	CNS - Seizures	Brevital (S), alfentanil, fentanyl
1819907	14 yr	Male	US	OT	NA	Cardiac – Arrhythmias	Zemuron (S), versed, fentanyl, pentothal, nitrous oxide
1837113	10 yr	Male	US	LT	10%	Hepatic – transaminitis	Propofol, sufentanil, nitrous oxide
1867264	15 yr	Female	US	NR	NA	Vascular – Hypertension	Propofol (S), alfentanil
1875277	11 yr	Female	US	OT	NA	Muscle disorder – Twitch	Zemuron (S), propofol, nitrous oxide, morphine, fentanyl
1913713	13 yr	Male	SE	HO	3%	Malignant hyperthermia	midazolam, fentanyl, propofol, vecuronium
1932425	12 yr	Female	US	LT	5-6%	Hepatic – transaminitis	Propofol , nitrous oxide, fentanyl,
1981234	1 yr	Male	BE	LT	8-10%	Cardiac - Arrhythmias	Propofol, Norcuron, Rapifen
3510768	14 mon	Female	US	LT	NA	Respiratory - bronchospasm	Raplon (S), lidocaine , propofol
3793139	7 yr	Female	US	OT	NA	Respiratory - bronchospasm	Rapacuronium (S), thiopental
3793169	8 yr	Male	US	OT	NA	Respiratory - bronchospasm	Rapacuronium (S), nitrous oxide, morphine, thiopental
4084905	16 yr	Female	US	HO	NA	Respiratory - laryngospasm	Zofran (S), propofol (S), fentanyl, midazolam, dexamethasone
4204585	8 yr	Male	DE	LT	NA	Respiratory – pulmonary edema	Remifentanil (S)
4329988	14 yr	Female	CA	RI	NA	Respiratory - apnea	Fentanyl (S) bupivacaine, lidocaine, propofol, rocuronium

<b>ISRNUM</b>	<b>AGE</b>	<b>SEX</b>	<b>Country</b>	<b>Outcome</b>	<b>Potency (Conc %)</b>	<b>EVENT</b>	<b>Concomitant medications (S) = suspect medications</b>
4334099	13 yr	Male	DE	HO	NA	Hepatic – transaminitis	Paracetamol, clexane
4454529	14 yr	Female	CA	OT	NA	Respiratory - apnea	Fentanyl (S), bupivacaine (S), lidocaine 2% with epinephrine(S), nitrous oxide, propofol, rocuronium
4457011	13 yr	Male	FR	LT	NA	Respiratory - bronchospasm	Augmentin (S), diprivan (S), sufenta (S)
4492495	13 yr	Male	US	LT	1-2%	Vascular - hypotension	Propofol, lidocaine, mivacurium
4691038	14 yr	Male	US	OT	NA	Hyperkalemia	Lidocaine (S), propofol (S), fentanyl (S), rocuronium
4848905	13 yr	Male	US	HO	12.4%	GI disorder - vomiting	Fentanyl, ondanestron, lidocaine, epinephrine
4848919	11 yr	Male	US	HO	9.20%	GI disorder - vomiting	Bupivacaine, cefazolin, morphine
5030756	16 yr	Male	NL	LT	NA	Cardiac – Cardiac arrest	Captopril, digoxin, alfentanil, propofol, rocuronium

\*\*Reported outcomes: DE=death, LT=life threatening, HO=hospitalization, RI=requiring intervention, OT=other, NR=not reported

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/s/

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