

One Year Post Exclusivity Adverse Event Review: Suprane (desflurane)

**Pediatric Advisory Committee Meeting
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**Hari Cheryl Sachs, MD, FAAP; Medical Officer
Pediatric and Maternal Health Staff
Office of New Drugs
Food and Drug Administration**



Outline

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Background Drug Information

- **Drug:** Suprane[®] (desflurane)
- **Therapeutic Category:** general inhalation anesthetic
- **Sponsor:** Baxter Healthcare Corp
- **Original Market Approval:** September 18, 1992
- **Pediatric Exclusivity Granted:** September 13, 2006
- **Labeling change:** Dec 15, 2006

Background Drug Information

Indications:

- Inhalation agent for induction and/or maintenance of anesthesia in in- and outpatient surgery (adults)
- Maintenance of anesthesia in intubated infants and children
- NOT recommended for induction of anesthesia in pediatric patients [or maintenance in non-intubated pediatric patients] due to high incidence of upper airway events.

Dosage:

- Individualized dose based on patient's response
- Tables provided with mean relative potency based on age (starting with 2 weeks of age)

Drug Use Trends: desflurane

Primarily purchased inpatient setting:

~85% sold into U.S. nonfederal hospital channels¹

Majority of use in adults²

- 37-38% of total unprojected discharges billed for general inhalation anesthetic
- Pediatric population <2-3% (~2,500 to 2,900 unprojected discharges/year)

Trend: No change pre- and post-exclusivity²

¹IMS Health, IMS Nationals Sales Perspectives™, Data extracted Oct 2007

²Premier Healthcare Informatics, RxMarket Advisor™, data provided Nov 2007



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Summaries of Medical and Clinical Pharmacology Reviews
of Pediatric Studies
as of January 15, 2008

Total Number of Drugs with Summaries Posted: 88

Summaries of Medical and Clinical Pharmacology Reviews

Drug	Sponsor	Review Summary	
Clofarabine - Clolar	Ilex	Medical	Clinical Pharmacology
Desflurane - Suprane	Baxter Healthcare Corporation	Medical	None*
Dorzolamide - Trusopt	Merck	Medical	None*
Emtricitabine - Emtriva	Gilead Sciences	Medical Medical	Clinical Pharmacology



Pediatric Exclusivity Study: desflurane

Safety study in 400 children, ages 2 to 16 years

After induction, received desflurane (n=300) or isoflurane (n=100) via laryngeal mask airway or facemask

Despite lower dose, incidence of major and minor respiratory AEs higher in desflurane arm, particularly for 2 to 6 year old cohort

All early discontinuations for AE occurred in desflurane arm

More patients in desflurane arm required treatment intervention (dexamethasone and propofol)

Labeling Changes: desflurane

Clinical Trials: Pediatric Surgery

“Not approved for maintenance of anesthesia in non-intubated pediatric patients due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm and secretions, seen in one study of maintenance of anesthesia in non-intubated pediatric patients.”

Indication and Usage

Warnings: Respiratory Adverse Reactions

Labeling Changes: desflurane

Pediatric Use:

High incidence of respiratory adverse reactions

laryngospasm (50%)

coughing (72%)

breathholding (68%)

increase in secretions (21%)

*oxyhemoglobin desaturation (26%)

*SpO₂ < 90%

Additional Relevant Safety Labeling: desflurane

Contraindication: sensitization to halogenated anesthetics

Warnings:

Perioperative Hyperkalemia- rare

- cardiac arrhythmias and death (post-operative period) in pediatric patients
- most vulnerable: latent or known neuromuscular disease (e.g., Duchenne muscular dystrophy)
- concomitant succinylcholine in most cases
- elevation of serum creatinine kinase and urine myoglobin levels

Malignant hyperthermia

Administration of Suprane- requires trained personnel, appropriate facilities and equipment

Additional Relevant Safety Labeling: desflurane

Precautions:

- Dose-dependent decreases in BP
- Increased HR (doses > 1 MAC)
- Recommendations for neurosurgery or cardiovascular surgery patients
- At high concentrations (>12%) may need to reduce nitrous to maintain adequate oxygen
- Hepatitis if sensitized to halogenated anesthetics

Additional Relevant Safety Labeling: desflurane

Adverse Events:

- Headache
- Bradycardia, HTN, nodal arrhythmia, tachycardia
- Nausea (27%), vomiting (16%)
- Increased salivation
- *Apnea, breathholding, *cough increased, *laryngospasm, pharyngitis
- Conjunctivitis (hyperemia)
 - *incidence 3 to 10%

Rare: hepatic failure and hepatic necrosis

Transient elevations glucose and/or WBC count

Adverse Event Reports since Market Approval (September 18, 1992): desflurane

Raw counts*	All reports (US)	Serious (US)	Death (US)
All ages	631 (387)	473 (265)	88 (39)
Adults (≥ 17)	488 (303)	392 (215)	81 (36)
Pediatrics (0-16)	47 (26)	39 (21)	5 (1)
Unknown Age	96 (58)	42 (29)	2 (2)

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

Unduplicated cases: 33 (3 fatalities)

Fatal Adverse Events (n=3) since Approval (Sept 18, 1992): : desflurane

- 9 yr old F during “leg surgery” switched to desflurane midway after induction with methohexital and isoflurane became severely hypoxic and bradycardic “at some point.” Rales on exam and pink frothy liquid from the endotracheal tube noted. Patient died 6 days after surgery from hypoxic brain damage

Labeling for these agents include respiratory depression, hypoxia and bradycardia

- 5 yr old F with meningomyelocele received desflurane, propofol, dopamine and piritramide* developed rhabdomyolysis (CK 200,000) 3 days after surgery and died 18 days after surgery

Labeling: elevation of serum creatinine kinase (CK) and urine myoglobin levels (desflurane: precautions); rhabdomyolysis (propofol: bolded warning)

*synthetic opioid used for post-operative analgesia in Europe

Fatal Adverse Event Reports since Approval (Sept 18, 1992): desflurane

- 5 mo F with fatal respiratory arrest 7 hours after general anesthesia with desflurane, atracurium besylate and propofol for I and D left thigh abscess related to vaccination (concomitant medication: amoxicillin clavulanate) Autopsy: necrotizing myopathy of diaphragm (possible underlying mitochondrial disorder)

Labeling for anesthetic agents includes need for administration by skilled individuals capable of supporting ventilation and use in monitored setting; high incidence of severe respiratory adverse events in pediatric patients (desflurane)

Adverse Event Reports during One-Year Post Exclusivity Period (Sept 2006 to Oct 2007): desflurane

Raw counts*	All reports (US)	Serious (US)	Death (US)
All ages	42 (7)	40 (5)	5 (1)
Adults (≥ 17)	30 (5)	28 (3)	2 (1)
Pediatrics (0-16)	6 (1)	6 (1)	3 (0)
Unknown Age	6 (1)	6 (1)	0

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

Unduplicated cases: 2 (1 fatalities)

Adverse Events during Pediatric Exclusivity Period: desflurane

2 unduplicated cases:

- Fatalities (n=1)
 - 5 month old with respiratory arrest and necrotizing myopathy of diaphragm (previously discussed)
- Nonfatal AEs (n =1)
 - 2 yr old F with artificial mitral valve developed prolonged coagulation time and bleeding 8 hours after surgery (acenocoumarol, propofol, midazolam, ketamine, sevoflurane, and desflurane)

Nonfatal Adverse Events (n=29) since approval: desflurane

- Malignant Hyperthermia- 3
- Cardiac disorders (arrest, arrhythmia)- 5
- Respiratory disorders (laryngospasm, bronchospasm, pulmonary edema, apnea)- 8
- Nervous system disorder (seizure)- 2
- Hepatic disorder (elevated transaminases)- 3
- Vascular disorders (hypo- or hypertension)- 4
- Gastrointestinal disorders (vomiting)- 2
- Electrolyte imbalance (hyperkalemia)- 1
- Muscle disorder (twitch)- 1

Underlined events are unlabeled for desflurane

Unlabeled Nonfatal Adverse Events

Since Approval: desflurane

Cardiac Arrest (n=3)

- 3 y/o M developed laryngospasm, bradycardia and cardiac arrest during general anesthesia for PE tubes; patient recovered after resuscitation (concomitant medications: propofol and fentanyl)
- 14 mo F developed 10 sec cardiac arrest after oxygen desaturation during anesthesia for supracondylar elbow fracture; patient recovered after atropine and ventilation (concomitant medications: rapacuronium, lidocaine, propofol and sevoflurane)
- 16 y/o M developed ventricular arrhythmia and then cardiac arrest after 4 hours of uneventful anesthesia with desflurane, recovered after epinephrine x 2 (concomitant medication: alfentanil, propofol, and rocuronium; PMHx: Duchenne muscular dystrophy [DMD], scoliosis, cardiomegaly, COPD, GERD)

Labeling for desflurane includes severe respiratory adverse events, the need for administration by skilled personnel in a monitored setting; Warning: cardiac arrhythmias and death related to hyperkalemia, particularly DMD patients; adverse events: arrhythmias

Unlabeled Nonfatal Adverse Events since Approval: desflurane Pulmonary Edema (n=1)

- 8 y/o M received desflurane and remifentanil during oral surgery; patient emerged from anesthesia rapidly and developed pulmonary edema after biting on airway

Labeling for desflurane includes warnings regarding severe respiratory AEs in pediatric patients, but not specifically pulmonary edema; pulmonary edema (remifentanil: adverse events <1%)

Unlabeled Non Fatal Adverse Events since Market Approval: desflurane Seizures (n=2)

- 6 week old M with VSD developed general seizures after pyloric stenosis surgery (anesthetic agents: desflurane and, succinylcholine, recovered after treatment with midazolam and thiopental)
- 16 y/o M developed tonic-clonic seizures and transient blindness while receiving test dose of methohexital while undergoing arthroscopy (concomitant medications: desflurane, fentanyl and alfentanil)

Labeling: blurred vision (fentanyl, alfentanil); seizures₂₁
(methohexital)

Summary: desflurane

- Labeling - not recommended for use in induction
- Labeling updated - not indicated for maintenance of anesthesia in non-intubated pediatric patients
- AEs incorporated: higher incidence of respiratory adverse reactions
- Although not explicitly described in labeling, several cases of cardiac arrest have been reported since marketing approval in both adults and pediatric patients.

FDA recommends revision of labeling to include as an adverse event, “cardiac arrest”.

FDA recommends routine monitoring of desflurane for AEs in all populations.

Does the Advisory Committee concur with these recommendations?

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