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Subject: Suprane[®] (Desflurane) BPCA Drug Use Review

Drug Name(s): Suprane[®] (Desflurane)

Application Type/Number: NDA 20-118

Applicant/sponsor: Baxter Healthcare Corporation

OSE RCM #: 2007-838

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EXECUTIVE SUMMARY

This consult examines drug utilization patterns for Suprane[®] (Desflurane), a general inhalation anesthetic, in the pediatric population, patients aged 0-16 years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on September 13, 2006. Since over 85% of Suprane[®] bottles were sold in U.S. non-federal hospital settings during the pre- and post-exclusivity periods, we focused on the inpatient setting. An inpatient proprietary drug use database licensed by FDA was used to examine the patterns of use for Suprane[®] during the three 12-month periods from October 1, 2004 through September 30, 2007.

For each of the three 12-month periods from October 1, 2004 through September 30, 2007, inpatient discharges with a billing for Suprane[®] (desflurane) represented approximately 37.5% of total discharges with a billing for general inhalation anesthetic, based on unprojected discharge data. Unprojected discharges for Suprane[®] in the pediatric population (ages 0-16 years) accounted for only small proportion of the total discharges for that product (less than 3%) during the pre- and post-exclusivity periods.

1 INTRODUCTION

1.1 REGULATORY HISTORY

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the review of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug soon after the one-year anniversary of granting exclusivity. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Suprane[®] (Desflurane) is a general inhalation anesthetic that is administered via vaporizer and is used for the induction and maintenance of general anesthesia for inpatient and outpatient surgery in adults and maintenance anesthesia in children. Suprane[®] is available as a 240 ml bottle and was approved on September 18, 1992.

Pediatric Exclusivity was granted on September 13, 2006. The supplemental new drug application, NDA 20-118/S-012 dated December 15, 2006, provided for the inclusion of data for the pediatric population (ages 2-16 years) as outlined in the FDA issued Pediatric Written request dated March 6, 2006.

NDA 20-118/S-012 provided for changes in the **Pediatric Surgery**, **WARNINGS**, and **PRECAUTIONS–Pediatric Use** sections of the labeling.

1.2 PRODUCT LABELING¹

Pediatric Surgery

SUPRANE (desflurane, USP) is not recommended for induction of anesthesia in pediatric patients because of the high incidence of moderate to severe upper airway adverse reactions, including laryngospasm, coughing, breathholding, and secretions, seen in studies of induction of anesthesia in pediatric patients. (see **WARNINGS and PRECAUTIONS – Pediatric Use**).

SUPRANE is 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. (see **WARNINGS and PRECAUTIONS – Pediatric Use**).

WARNINGS

Perioperative Hyperkalemia

Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the postoperative period. Patients with latent as well as neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatinine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Respiratory Adverse Reactions in Pediatric Patients

SUPRANE (desflurane, USP) is not recommended for induction of general anesthesia via mask in children due to a high incidence of moderate to severe respiratory adverse reactions seen in clinical studies (see **PRECAUTIONS – Pediatric Use**).

SUPRANE is not approved for maintenance of anesthesia in non-intubated children due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm and secretions (see **PRECAUTIONS – Pediatric Use**).

PRECAUTIONS

Pediatric Use

SUPRANE (desflurane, USP) is approved for maintenance of anesthesia in infants and children after induction of anesthesia with agents other than SUPRANE, and tracheal intubation.

SUPRANE 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 (SpO₂ <90%) (26%) seen in clinical studies.

SUPRANE is not approved for maintenance of anesthesia in non-intubated children due to an increased incidence of respiratory adverse reactions (see below).

In a clinical safety trial conducted in children aged 2 to 16 years (mean 7.4 years),

¹ Suprane[®] (Desflurane), **package insert**, Baxter Healthcare Corporation, Deerfield, IL. Accessed 1-3-08 via <http://www.fda.gov/medwatch/safety/2006/dec06.htm>

following induction with another agent, SUPRANE and isoflurane (in N2O/O2) 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.

**MAINTENANCE IN NONINTUBATED PEDIATRIC PATIENTS
(FACE MASK OR LMA USED; N=300)**

All Respiratory Events* (>1% of All Pediatric Patients)				
	All Ages (N=300)	2-6 yr (N=150)	7-11 yr (N=81)	12-16 yr (N=69)
Any respiratory events	39%	42%	33%	39%
Airway obstruction	4%	5%	4%	3%
Breath-holding	3%	2%	3%	4%
Coughing	26%	33%	19%	22%
Laryngospasm	13%	16%	7%	13%
Secretion	12%	13%	10%	12%
Non-specific desaturation	2%	2%	1%	1%

*Minor, moderate and severe respiratory events

SUPRANE 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.* SpO2 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.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

Using the currently available data resources, this review describes inpatient drug use patterns for Suprane® in the pediatric population as well as in the adult population and includes data for three 12-month periods starting two years before and one year following the granting of pediatric exclusivity on September 13, 2006. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

2.2 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ data (*see Appendix*) were used to determine the setting in which Suprane® was sold. Sales of this product by number of bottles of solution (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from October 1, 2004 – September 30, 2007 (*data not provided*).²

During the three 12-month periods of this review, non-federal hospitals accounted for the majority of Suprane® sales (~87 %). Thus, the examination of Suprane® utilization patterns focused on the inpatient setting. It should be noted that Suprane® and Ultane® (Sevoflurane) each represented approximately 41% of sales for the selected market of the USC class 04230 (Anesthetic, general other inhalation).

2.3 DATA SOURCES USED

We used data from Premier Healthcare Informatics, RxMarket Advisor™ to examine inpatient utilization patterns for unprojected discharges associated with a billing for desflurane, sevoflurane, enflurane, and isoflurane, stratified by ages 0-1 yr, 2-6 yrs, 7-11 yrs, and 12-16 yrs for the time period from October 1, 2004 through September 30, 2007.

2.4 PRODUCTS INCLUDED

In addition to examining inpatient drug utilization patterns for Suprane®, we examined inpatient utilization patterns for other general inhalation anesthetics. These products were selected based on their indication and dosage form. Comparator products analyzed include Enthrane® (enflurane), Forane® (isoflurane), and Ultane® (sevoflurane).

3 RESULTS

3.1 INPATIENT DATA (UNPROJECTED DISCHARGES)

On average, during the three 12-month periods from October 1, 2004 through September 30, 2007, inpatient discharges with a billing for Suprane® (desflurane) represented approximately 37.5% of total discharges with a billing for general inhalation anesthetic, based on unprojected discharge data (*Table 1*). Ultane® (sevoflurane) represented 45%, Forane® (isoflurane) represented approximately 17%, and Enthrane® (enflurane) represented less than 1%.

Inpatient discharges with a billing for Suprane® for the pediatric population accounted for less than 3% (average 2,703 discharges) of the total inpatient unprojected discharge data with a billing for Suprane® in each of the three 12-month periods from October 1, 2004 through September 30, 2007 (*Table 1*).

² IMS Health, IMS National Sales Perspectives™, Data extracted 10-24-2007, Source file: 0710des.DVR

Table 1.

Number of UNPROJECTED DISCHARGES Associated with a Hospital Billing for Select Inhalation Anesthetics (desflurane, sevoflurane, enflurane, and isoflurane) from October 1, 2004 – September 30, 2007

	October 1, 2004- September 30, 2005		October 1, 2005- September 30, 2006		October 1, 2006- September 30, 2007	
	Unprojected discharges	share (%)	Unprojected discharges	share (%)	Unprojected discharges	share (%)
TOTAL	282,135	100	303,463	100	258,432	100
DESFLURANE	103,835	37	114,439	38	97,852	38
0-16 years	2,517	2	2,893	2.5	2,698	3
<i>0-1 years</i>	<i>386</i>	<i>0.4</i>	<i>441</i>	<i>0.4</i>	<i>474</i>	<i>0.5</i>
<i>2-6 years</i>	<i>342</i>	<i>0.3</i>	<i>423</i>	<i>0.4</i>	<i>433</i>	<i>0.4</i>
<i>7-11 years</i>	<i>511</i>	<i>0.5</i>	<i>628</i>	<i>0.5</i>	<i>570</i>	<i>0.6</i>
<i>12-16 years</i>	<i>1,278</i>	<i>1.2</i>	<i>1,401</i>	<i>1.2</i>	<i>1,221</i>	<i>1.2</i>
17+ years	101,318	98	111,546	97.5	95,154	97
ENFLURANE	62	0.0	1,686	0.6	1,528	0.6
0-16 years	2	3	17	1	19	1
<i>0-1 years</i>	<i>1.0</i>	<i>1.6</i>	<i>3.0</i>	<i>0.2</i>	<i>6.0</i>	<i>0.4</i>
<i>2-6 years</i>	<i>1.0</i>	<i>1.6</i>	<i>5.0</i>	<i>0.3</i>	<i>3.0</i>	<i>0.2</i>
<i>7-11 years</i>	<i>0</i>	<i>0</i>	<i>3.0</i>	<i>0.2</i>	<i>3.0</i>	<i>0.2</i>
<i>12-16 years</i>	<i>0</i>	<i>0</i>	<i>6.0</i>	<i>0.4</i>	<i>7.0</i>	<i>0.5</i>
17+ years	60	97	1,669	99	1,509	99
ISOFLURANE	58,406	21	50,845	17	36,301	14
0-16 years	1,400	2	1,354	3	1,210	3
<i>0-1 years</i>	<i>459</i>	<i>0.8</i>	<i>455</i>	<i>0.9</i>	<i>449</i>	<i>1.2</i>
<i>2-6 years</i>	<i>189</i>	<i>0.3</i>	<i>215</i>	<i>0.5</i>	<i>218</i>	<i>0.6</i>
<i>7-11 years</i>	<i>239</i>	<i>0.4</i>	<i>231</i>	<i>0.5</i>	<i>185</i>	<i>0.5</i>
<i>12-16 years</i>	<i>513</i>	<i>0.9</i>	<i>453</i>	<i>0.9</i>	<i>358</i>	<i>1.0</i>
17+ years	57,006	98	49,491	97	35,091	97
SEVOFLURANE	119,832	42.5	136,493	45	122,751	47.5
0-16 years	5,449	5	6,520	5	6,350	5
<i>0-1 years</i>	<i>1,522</i>	<i>1.0</i>	<i>1,879</i>	<i>1.0</i>	<i>2,062</i>	<i>1.7</i>
<i>2-6 years</i>	<i>1,194</i>	<i>1.0</i>	<i>1,489</i>	<i>1.0</i>	<i>1,478</i>	<i>1.2</i>
<i>7-11 years</i>	<i>1,061</i>	<i>1.0</i>	<i>1,286</i>	<i>1.0</i>	<i>1,206</i>	<i>1.0</i>
<i>12-16 years</i>	<i>1,672</i>	<i>1.0</i>	<i>1,866</i>	<i>1.0</i>	<i>1,604</i>	<i>1.3</i>
17+ years	114,383	95	129,973	95	116,401	95

Premier Healthcare Informatics, RxMarket Advisor™, data provided by Premier November 15, 2007.

Source file: 2006-838 Premier 11-1-07 desflurane BPCA.xls

4 DISCUSSION

Based on the databases employed for this analysis, Suprane® represented approximately one-third of the selected market of general inhalation anesthetics. Unprojected discharges for Suprane® in the pediatric population (ages 0-16 years) accounted for only small proportion of the total discharges for that product during the pre- and post-exclusivity periods.

Generally, we found that discharges associated with general inhalation anesthetics in the pediatric population accounted for only small proportion of the discharges for all ages.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that desflurane is distributed primarily in inpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. The inpatient data are based on unprojected patient counts from hospitals in the Premier Hospital network using Premier Healthcare Informatics, RxMarket Advisor™ and any observed changes in absolute patient counts do not necessarily represent national trends and should be interpreted with caution.

5 CONCLUSION

The proportion of inpatient discharges with a billing for Suprane® represented approximately 37.5% of total discharges with a billing for general inhalation anesthetic and has not been changed from the pre- to the post-exclusivity period (October 1, 2005- September 30, 2006 and October 1, 2006- September 30, 2007, respectively).

Nationally unprojected discharges for Suprane® in the pediatric population (ages 0-16 years) accounted for only small proportion of the total discharges for that product (less than 3%) during the pre- and post-exclusivity periods.

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APPENDICES

APPENDIX 1: Database Descriptions

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.

Premier RxMarket Advisor

Premier's database is a large hospital drug utilization and financial database. Information is available from over 590 acute care and pediatric facilities and includes approximately 38 million inpatient records. On an annual basis, this constitutes roughly one out of every six inpatient discharges in the United States. Data are available from January 2000 through the present, but have a lag time of approximately 75 days. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, the Premier Informatics group developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, bed size, population served, payors and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. Based upon these analyses, FDA believes that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommends making this determination on a drug-specific basis.

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