CLINICAL REVIEW

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Reviewer Name	Robert B. Shibuya, M.D.
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Established Name	Desflurane
Trade Name	Suprane
Therapeutic Class	Inhaled Anesthetic
Applicant	Baxter
Priority Designation	S
Formulation	Liquid for vaporization
Dosing Regimen	PRN
Indication	General anesthesia
Intended Population	Adults and children

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical data submitted in this supplement demonstrated a marked increase in the incidence of both major (associated with significant oxygen desaturation) and minor respiratory events including laryngospasm, airway obstruction, secretions, and breath holding in non-intubated pediatric patients who underwent maintenance anesthesia with desflurane compared to a cohort of children treated similarly with isoflurane. The incidence of these respiratory events appeared to be related to the inspired concentration of desflurane.

Assuming that acceptable language regarding the results of the submitted study can be negotiated, this reviewer recommends that this labeling supplement be approved.

1.2 Recommendation on Postmarketing Actions

Not applicable.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Desflurane is an inhaled anesthetic that was initially approved in 1992. It is currently approved in adults for the induction and maintenance of anesthesia. In children, it is approved for maintenance anesthesia in intubated children. The reason for the more limited indication in children is that desflurane has been recognized as being more pungent and irritating than similar agents (sevoflurane and isoflurane), particularly in children. Therefore, it is only labeled for use in intubated children, where the airway is protected.

The Agency wanted data to further address the tolerability of desflurane in children. To meet the requirements of the Agency's Pediatric Written Request (PWR), the applicant has completed one adequate and well-controlled study in children aged 2-16 years to evaluate the safety of desflurane used for the maintenance of anesthesia in non-intubated children. The pediatric program, as stipulated in the PWR, initially planned to evaluate the safety of desflurane in children down to age 1 month. However, after it became apparent that the incidence of severe respiratory adverse events was highest in the youngest age stratum (2-6 years old) for desflurane, a second planned study in children aged 1 month to 2 years was cancelled at the Division's request and the PWR so modified.

Therefore, the response to the Agency's Pediatric Written Request for desflurane consists of one study.

1.3.2 Efficacy

The study currently submitted did not assess efficacy.

1.3.3 Safety

Study 32,363-002 evaluated a total of 400 children aged 2-16 years. Three hundred patients received maintenance anesthesia by laryngeal mask airway (LMA) or facemask (FM) using desflurane and 100 received anesthesia by LMA or FM using isoflurane. Patients were stratified into three groups: 2-6 years old, 7-11 years old, and 12-16 years old. The study was designed to evaluate the incidence of major respiratory events between the treatment arms. Study drug was administered single-blind.

After review of the clinical trial data, this reviewer concluded the following.

1. The incidence of major and minor respiratory events was higher in the desflurane cohort (particularly in the 2-6 year old stratum) which was the primary study endpoint.
2. The difference in raw respiratory adverse event rates is supported by complementary observations.
    a. All early discontinuations (for adverse events) occurred in the desflurane arm.
    b. Intraoperatively, a greater proportion of patients required treatment with dexamethasone and propofol in the desflurane cohort than those patients treated with isoflurane, predominantly to manage adverse events.
3. The incidence of adverse events in the desflurane arm may be underestimated.
    a. Patients randomized to desflurane received, on average, lower doses of study drug compared to the isoflurane cohort [on the basis of the proportion of mean alveolar concentration (MAC)]. This finding is relevant to the interpretation of the adverse event rate because the study data suggest that respiratory events are correlated with increasing inspired concentrations of desflurane. Since the patients in the desflurane cohort were exposed to lower concentrations of drug, it is not unreasonable to suggest that the adverse event rate might have been higher in the desflurane cohort if the MAC proportions were matched between treatment arms.

   b. The study was single-blind where only the patient was blinded to the identity of the study drug.
4. Other observations.
   a. Respiratory events occurred during all phases of anesthesia (post-induction, maintenance, and emergence).
   b. The serious adverse events (SAEs) did not appear to be drug-related. However all three of the SAEs occurred in the desflurane cohort.
   c. The non-serious adverse events, other than the respiratory events, appeared matched in the desflurane and isoflurane cohorts and were typical of an inhaled anesthetic and in a post-surgical pediatric population.

1.3.4 Dosing Regimen and Administration

The dose [minimum alveolar concentration (MAC) or concentration at which 50% of people will tolerate an incision] has been established for desflurane. The package insert limits the use of desflurane to "...persons trained in the administration of general anesthesia...Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available." There are no changes to the Dosage and Administration section of the label as a result of this supplement.

1.3.5 Drug-Drug Interactions

Desflurane is not metabolized. As a central nervous system (CNS) depressant, it must be used with caution in concert with other CNS active drugs.

1.3.6 Special Populations

As previously noted, this study was initiated to further define the tolerability of desflurane in children.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

SUPRANE (desflurane) was initially approved in 1992 as an inhaled anesthetic agent for induction and or maintenance of anesthesia for inpatient and outpatient surgery in adults. The current package insert states "SUPRANE (desflurane, USP) is not recommended for induction of anesthesia in pediatric patients because of a high incidence of moderate to severe upper airway adverse events (see WARNINGS). After induction of anesthesia with agents other than SUPRANE, and tracheal intubation, SUPRANE is indicated for maintenance of anesthesia in infants and children.

2.2 Currently Available Treatment for Indications

Inhaled anesthetics approved for use in children include sevoflurane, isoflurane, halothane, and enflurane.

2.3 Availability of Proposed Active Ingredient in the United States

Desflurane is currently approved and available for induction and maintenance in adults and maintenance in intubated children.

2.4 Important Issues With Pharmacologically Related Products

None.

2.5 Presubmission Regulatory Activity

The initial Pediatric Written Request (PWR) was issued on December 31, 2001. That request required two studies very similar to the subject of this submission (Study 32,363-002). The two studies outlined in the PWR were essentially identical to each other with the exception of the ages of the children to be studied. One study was to enroll patients ages 2-16 years; the other was to enroll patients ages 1 month to 2 years.

On June 20, 2003, the PWR was amended as follows:

- The Division permitted the design to be single-blind (investigator unblinded) for technical issues (requirement for separate gas analyzers and different minimal alveolar concentrations).
- The mode of ventilation was to be specified prior to randomization.
- The date for study submission was changed.

Study 32,363-002 (which enrolled patients aged 2- 16 years) was conducted between February and June 2004. The applicant analyzed the study data and found that the rates of severe respiratory adverse events (specifically laryngospasm) were highest in the youngest age stratum (ages 2-6) for the desflurane cohort. After consultation with the Division, to protect the safety of the study population, the requirement for the second study (enrolling patients aged 1 month to 2 years) was dropped. A third PWR, reflecting this, was issued on March 6, 2006.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

No Chemistry/Manufacturing/Controls or Pharmacology/Toxicology information was submitted.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This supplement contains data from a single clinical trial, Study 32,363-002. The applicant has provided a full clinical study report, the SAS transport files, and appropriate, required narratives and case report forms. All submitted material was reviewed.

4.2 Tables of Clinical Studies

Because only one study was submitted, this section is unnecessary.

4.3 Review Strategy

Data submitted for Study 32,363-002 and pertinent literature were reviewed.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) has provided the preliminary results from two investigators, Susan Verghese, M.D. and Gregory Hammer, M.D. who enrolled the largest numbers of patients into the study. The preliminary findings from DSI indicate that there no significant issues with the study conduct or data integrity.

4.5 Compliance with Good Clinical Practices

The applicant has certified that the study was conducted in accordance with Good Clinical Practices as defined in International Conference on Harmonization guidelines and the Declaration of Helsinki.

4.6 Financial Disclosures

In the Form FDA 356h, the applicant certified that no financial arrangements had been made which may have affected the outcome of the study.

5 CLINICAL PHARMACOLOGY

No clinical pharmacology data were submitted.

6 INTEGRATED REVIEW OF EFFICACY

No efficacy data were submitted.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of the proposed additional labeling, Baxter has conducted the one clinical study and has included 10 journal articles to complement the data submitted. The applicant has conducted descriptive statistics for the respiratory events and other safety data stratified by age groups (2-6 years old, 7-11 years old, and 12-16 years old) and, usually, in aggregate.

The applicant has also conducted exploratory analyses of the co-variables (e.g. type of airway (LMA or facemask), mode of ventilation (controlled, assisted, or spontaneous), etc.).

After review of the clinical trial data, this reviewer concluded the following. A discussion of the conclusion/observation is contained in this review as referenced in *italics* following the statement.

1. The incidence of major and minor respiratory events was higher in the desflurane cohort (particularly in the 2-6 year old stratum) which was the primary study endpoint. *Section 7.1.3.3*
2. The difference in raw respiratory adverse event rates is supported by complementary observations.
    a. All early discontinuations (for adverse events) occurred in the desflurane arm. *Section 7.1.3*
    b. Intraoperatively, a greater proportion of patients required treatment with dexamethasone and propofol in the desflurane cohort than those patients treated with isoflurane, predominantly to manage adverse events. *Section 7.1.4*
3. The incidence of adverse events in the desflurane arm may be underestimated.
    a. Patients randomized to desflurane received, on average, lower doses of study drug compared to the isoflurane cohort [on the basis of the proportion of mean alveolar concentration (MAC)]. *Table 10, Section 7.1.3.3* This finding is relevant to the interpretation of the adverse event rate because the study data suggest that

respiratory events are correlated with increasing inspired concentrations of desflurane. *Table 11, Section 7.1.3.3* Since the patients in the desflurane cohort were exposed to lower concentrations of drug, it is not unreasonable to suggest that the adverse event rate might have been higher in the desflurane cohort if the MAC proportions were matched between treatment arms.

b. The study was single-blind where only the patient was blinded to the identity of the study drug. *Description of protocol-appendix to this review*

4. Other observations.
    a. Respiratory events occurred during all phases of anesthesia (post-induction, maintenance, and emergence). *Table 9, Section 7.1.3.3*
    b. The serious adverse events (SAEs) did not appear to be drug-related. However all three of the SAEs occurred in the desflurane cohort. *Section 7.1.2*
    c. The non-serious adverse events, other than the respiratory events, appeared matched in the desflurane and isoflurane cohorts and were typical of an inhaled anesthetic and in a post-surgical pediatric population. *Section 7.1.5.4*

7.1.1 Deaths

There were no deaths.

7.1.2 Other Serious Adverse Events

While on study, three serious adverse events were documented, all in the desflurane group. Narratives follow.

Patient 02-008 –Sinus Tachycardia
This is a 5 year-old girl with no relevant past medical history who presented with a supracondylar fracture of the humerus requiring open reduction and fixation in the operating room. Vital signs in the holding area were blood pressure 114/60, heart rate 110, oxygen saturation 100%.

This patient inhaled sevoflurane for induction and she was maintained on desflurane/nitrous oxide with a LMA. Desflurane was started at 12:56 PM and stopped at 14:44. Intraoperative blood pressure and oxygen saturation were within normal limits. The heart rate ranged from 113 to 135 intraoperatively. The tachycardia was noted 30 minutes into the case and persisted throughout the case. The patient received cefazolin, ondansetron, morphine, ibuprofen, and oxycodone during the operative and immediate post-operative periods.

Tachycardia (to 144 bpm) persisted for 26 hours following emergence whereupon it spontaneously resolved without sequelae. The patient's hospitalization required prolongation to monitor the tachycardia. The investigator opined that the tachycardia could have been due to postoperative pain but could not rule an effect of the desflurane.

Patient 07-013 – Nausea and vomiting
This is an 11-year-old boy who underwent an inguinal herniorrhaphy. Intravenous propofol was used for induction and he was maintained on desflurane/nitrous oxide. The duration of anesthesia was 47 minutes. His vital signs were stable intra and post-operatively. Approximately 2 hours and 20 minutes following the end of surgery, the patient experienced five episodes of vomiting treated with dolasetron, ondansetron, and hydroxysine. His hospitalization was prolonged to manage the vomiting. The investigator opined that the nausea and vomiting were possibly due to study drug.

Patient 07-015 – Vomiting
This is a 13-year-old boy with a history of attention deficit hyperactivity disorder and tympanic membrane perforation. He underwent tympanoplasty (after induction with intravenous propofol and inhaled sevoflurane and nitrous oxide/desflurane for maintenance). The duration of surgery was 1 hour and 15 minutes. Within 15 minutes of the end of anesthesia, the patient began vomiting (x 6). The vomiting was managed with dolasetron and ondanestron and resolved approximately 8 hours later. Because the vomiting extended the hospitalization, this event met the definition of "serious." The investigator thought the vomiting was possibly associated with study drug.

Serious Adverse Event Post End-of-Study: One day following a circumcision and hospital discharge (defined as end-of study), one patient (treated with isoflurane) experienced wound dehiscence and required surgical revision to the circumcision site. The investigator considered this SAE not related to study drug.

7.1.3 Dropouts and Other Significant Adverse Events

Six patients discontinued for adverse events, all in the desflurane cohort.

Patient 01-021 – Laryngospasm
This is a 6-year-old boy with a past medical history significant for environmental allergies who underwent inguinal herniorrhaphy. He was induced with sevoflurane and maintained on desflurane/nitrous oxide. Twenty-five minutes after the start of desflurane, the patient experienced severe laryngospasm. Desflurane was discontinued and the patient was intubated after neuromuscular blockade and deepening anesthesia with propofol. At the time of the event, the surgery was complete. The patient was having the desflurane uptitrated for a deep LMA removal. The investigator opined that the event was probably due to the study drug.

Patient 05-002 – Coughing
This is a 2 3/4-year-old girl with no relevant past medical history. She underwent inguinal herniorrhaphy after induction with sevoflurane. Eighteen minutes after the initiation of maintenance anesthesia with desflurane and nitrous oxide, the patient experienced severe laryngospasm and moderate cough lasting 90 and 30 seconds, respectively. The events were treated with positive pressure ventilation and jaw thrust. Again, these events occurred with uptitration for a deep LMA removal.

Patient 07-007 – Coughing
This is a 5 ½ year old girl with patellofemoral syndrome who underwent a lateral knee release. She was induced with propofol and maintained with desflurane/nitrous oxide. At the end of the case, as the desflurane was being uptitrated for a deep LMA removal, the patient experienced 80 seconds of moderate to severe cough and two episodes of mild cough several minutes later.

Patient 13-004 – Airway Obstruction
This is a 13 ½ year-old male with a history of asthma who underwent a herniorrhaphy. Anesthesia was induced with propofol and maintained with desflurane/nitrous oxide. After 5 minutes on desflurane, the patient experienced mild bronchospasm which lasted for 7 minutes and 15 seconds. Moderate airway obstruction and mild cough occurred simultaneously. Desflurane was discontinued and sevoflurane used successfully to complete the surgery.

Patient 14-003 – Breath-holding, coughing
This is a 17-year-old male who underwent removal of orthopedic hardware after propofol induction. Maintenance anesthesia was desflurane/nitrous oxide. Four minutes after the start of desflurane, severe cough and secretions were noted as well as moderate breath holding which lasted up to 3 minutes. Desflurane was immediately discontinued and the case was completed using isoflurane for anesthesia. The respiratory signs were treated with propofol and fentanyl.

Patient 15-006 – Bronchospasm
This is a 3 ½ year old boy with a history of food allergies who underwent herniorrhaphy. Anesthesia was induced with sevoflurane. At 15 minutes into the case, the inspired desflurane concentration was 4.0%. Twenty four minutes after the start of desflurane for maintenance, the patient experienced severe desaturation lasting 5 minutes and treated with positive pressure ventilation. The inspired desflurane concentration at this time was approximately 5.9%. Twenty one minutes following the episode of desaturation, two minutes of severe bronchospasm were noted (inspired desflurane concentration was 10.9%). The desflurane was discontinued shortly thereafter and the patient was switched to sevoflurane. Later in the case, mild secretions were noted.

7.1.3.1 Overall profile of dropouts

A total of 10 (of 410) patients who were eligible for the study did not receive study drug. The reasons for this were not related to the study drug itself (need to a surgical position that required intubation, surgery cancelled, etc.).

7.1.3.2 Adverse events associated with dropouts

The six patients (all desflurane treated) who prematurely discontinued, all did so due to respiratory events and are discussed in 7.1.3 above.

7.1.3.3 Other significant adverse events

Major Respiratory Events

The primary objective of the study was to determine the incidence of "major" respiratory events in non-intubated children maintained on desflurane or isoflurane. As such, the respiratory adverse events are of primary importance for this application.

As discussed in more detail in the Appendix to this review, the applicant defined a grading system for the respiratory events which encompassed eight categories: Airway obstruction, Breath-holding, Bronchospasm, Coughing, Laryngospasm, Secretions, Hiccups, and Oxygen Desaturation due to an undefined cause. Each category had a categorical severity definition ranging from "Mild" to "Moderate" to "Severe." The severity definitions were specific to the category although, to meet the definition of "severe," patients had to desaturate < 90% for > 15 seconds or require tracheal intubation for all categories.

A "major" respiratory event was defined as any "severe" event or desaturation due to an undefined cause. Table 1 summarizes the percentage of all patients who experienced a major event.

Table 1: Percent of patients experiencing a major respiratory event (all patients)

	Desflurane (N = 300)	Isoflurane (N = 100)
Any event	9%	4%
Airway Obstruction	0.3%	0%
Breath Holding	1.3%	0%
Bronchospasm	0%	0%
Coughing	2%	1%
Hiccups	0%	0%
Laryngospasm	5.3%	2%
Secretions	1.3%	2%
Non-specific Desaturation	1.7%	1%

The following Tables (2-4) summarize the major events by age stratum. These data show that, for desflurane, the major driver for the difference in incidence was the youngest age stratum (Table 2).

Table 2: Percent of patients experiencing a major respiratory event (ages 2-6 years)

	Desflurane (N = 150)	Isoflurane (N = 51)
Any event	13.3%	4%
Airway Obstruction	0%	0%
Breath Holding	1.3%	0%
Bronchospasm	0%	0%
Coughing	2%	1%
Hiccups	0%	0%
Laryngospasm	9.3%	1%
Secretions	1.3%	1%
Non-specific Desaturation	2%	1%

Table 3: Percent of patients experiencing a major respiratory event (ages 7-11 years)

	Desflurane (N = 81)	Isoflurane (N = 27)
Any event	3.7%	7%**
Airway Obstruction	1.2%	0%
Breath Holding	1.2%	0%
Bronchospasm	0%	0%
Coughing	1.2%	0%
Hiccups	0%	0%
Laryngospasm	1.2%	4%*
Secretions	0%	4%*
Non-specific Desaturation	1.2%	0%

* 2 patients experienced these AEs

** 1 patient experienced this AE

Table 4: Percent of patients experiencing a major respiratory event (ages 12-16 years)

	Desflurane (N = 69)	Isoflurane (N = 22)
Any event	5.8%	0%
Airway Obstruction	0%	0%
Breath Holding	1.4%	0%
Bronchospasm	0%	0%
Coughing	2.9%	0%
Hiccups	0%	0%
Laryngospasm	1.4%	0%
Secretions	2.9%	0%
Non-specific Desaturation	1.4%	0%

Respiratory Events (major and non-major)

The applicant also collected data on respiratory events that did not meet the definition of "major" (desaturation < 90% for > 15 seconds). The following tables show the percentage of patients in each indicated group who suffered any respiratory event, regardless of severity. These tables

were generated by reorganizing the data from applicant's Table 28 for easier comparison. The data show that, for the aggregate data (Table 5) and data stratified by age (Tables 6-8), the incidence of respiratory events was higher in the desflurane cohort than the isoflurane cohort and support the findings for the major respiratory events.

Table 5: Percent of patients experiencing any respiratory event (all ages)

	Desflurane (N = 300)	Isoflurane (N = 100)
Any event	39%	27%
Airway Obstruction	4%	5%
Breath Holding	3%	1%
Bronchospasm	1%	1%
Coughing	26%	14%
Hiccups	1%	0%
Laryngospasm	13%	5%
Secretions	12%	12%
Non-specific Desaturation	2%	1%

Table 6: Percent of patients experiencing any respiratory event (ages 2-6)

	Desflurane (N = 150)	Isoflurane (N = 51)
Any event	42%	35%
Airway Obstruction	5%	10%
Breath Holding	2%	2%
Bronchospasm	1%	2%
Coughing	33%	18%
Hiccups	1%	0%
Laryngospasm	16%	6%
Secretions	13%	16%
Non-specific Desaturation	2%	2%

Table 7: Percent of patients experiencing any respiratory event (ages 7-11)

	Desflurane (N = 81)	Isoflurane (N = 27)
Any event	33%	26%
Airway Obstruction	4%	0%
Breath Holding	3%	0%
Bronchospasm	1%	0%
Coughing	19%	15%
Hiccups	1%	0%
Laryngospasm	7%	7%
Secretions	10%	7%
Non-specific Desaturation	1%	0%

Table 8: Percent of patients experiencing any respiratory event (ages 12-16)

	Desflurane (N = 69)	Isoflurane (N = 22)
Any event	39%	9%
Airway Obstruction	3%	0%
Breath Holding	4%	0%
Bronchospasm	1%	0%
Coughing	22%	5%
Hiccups	0%	0%
Laryngospasm	13%	0%
Secretions	12%	9%
Non-specific Desaturation	1%	0%

The following table (9) is reorganized from the applicant's Tables 20, 21, and 22. It shows that major respiratory events occurred at all phases while the study drug was being administered. This information is complimentary to the published literature[1].

Table 9: Percent of desflurane-treated patients experiencing a major respiratory event at a given phase of anesthesia (N = 300)

	Post-Induction	Maintenance	Emergence
Any event	9%	5.3%	4%
Airway Obstruction	0.3%	0%	0.3%
Breath Holding	1.3%	1%	0.7%
Bronchospasm	0%	0%	0%
Coughing	2%	1.3%	0.7%
Hiccups	0%	0%	0%
Laryngospasm	5.3%	2.7%	3%
Secretions	1.3%	0.7%	0.7%
Non-specific Desaturation	1.7%	0.7%	0%

In evaluating the incidence of respiratory events in the desflurane arm, one other fact should be noted. Table 16 of the clinical study report (identified as Table 10 in this review) was extracted from page 59 of the study report. This table shows the descriptive statistics for the minimal alveolar concentration of study drug for the desflurane and isoflurane cohorts. These data show that, while the mean duration of exposure to the two agents was the same, on average, the desflurane cohort was exposed to a lower effective dose of study drug (based upon the proportion of minimal alveolar concentration). Therefore, if respiratory events are correlated with anesthetic exposure, it follows that the respiratory event rate in the desflurane cohort may be underestimated compared to the isoflurane cohort.

Table 10: Exposures to inhaled anesthetic

Variable	Statistic	Desflurane (N = 300)	Isoflurane (N = 100)
Duration (minutes)	N	300	100
	Mean	49	49
	St. Dev	32	34
Average end-tidal concentration (MAC)	N	299	100
	Mean	0.7	0.8
	St. Dev	0.2	0.3
Minimal end-tidal concentration (MAC)	N	299	100
	Mean	0.5	0.6
	St. Dev	0.2	0.3
Maximum end-tidal concentration (MAC)	N	299	100
	Mean	0.8	1.0
	St. Dev	0.3	0.3

Major Respiratory Events Appear Correlated with increasing Desflurane concentration

A. Inspired desflurane concentrations at time of respiratory event(s)

Because the inspired concentration of anesthetic gas has to be titrated during the case depending on noxious stimuli and hemodynamic parameters, a conventional dose:adverse event correlation is not the best method of exploring the relationship between anesthetic dose and adverse events.

In order to assess the dose dependence of the respiratory event rate, this reviewer conducted the following analysis. Patients who had experienced major respiratory events were identified in the respirat.xpt dataset. The time of onset of the major respiratory event(s) was noted. Then, this reviewer identified the inspired anesthetic concentrations prior to the onset of the respiratory event(s) and the concentration(s) documented around the time of the event(s) from the hrparam.xpt dataset. Because the protocol required documentation of the inspired anesthetic concentration only every 15 minutes, in most cases, the time of the respiratory event and documented inspired concentration do not exactly coincide so some estimation was required.

For 13 of the 27 desflurane-treated patients who experienced a major respiratory event, there was documentation that the desflurane concentration had been increased around the time of the onset of the event. By comparison, for none of the isoflurane-treated patients who experienced a major event did it appear that the event was associated with an increase in inspired isoflurane concentration. These data are summarized in Table 11 below.

Table 11: Cases where the onset of major respiratory events was associated with a documented increase in the concentration of inhaled anesthetic

Study Drug	Resp Event Associated with ↑ in inspired anesthetic concentration (# of patients)	Resp Event Not Associated with ↑ in inspired anesthetic concentration (# of patients)	No Data
Desflurane	13	11*	3
Isoflurane	0	4**	0

*The available data (inspired desflurane concentration documented every 15 minutes) showed that the event was not associated with an increase in desflurane concentration or may be equivocal

**For all 4 patients, it was clear that the isoflurane concentration was unchanged or lower at the time of the event.

B. Discontinuations for respiratory events occurred during uptitration for deep LMA removal

The dose-dependence of the respiratory events for desflurane is supported by another observation. As noted in section 7.1.3, for the best documented respiratory events (early terminations for the respiratory event), the event occurred during or following an increase in the concentration of desflurane in at least 4/6 cases (inadequate data for the other two cases).

Furthermore, this reviewer notes that, in the desflurane cohort, the incidence of respiratory events was higher for deep LMA removal compared to awake LMA removal. This is contrary to what is expected. The isoflurane cohort showed the expected pattern (more respiratory events with awake LMA removal than deep removal). These data are summarized below (Table 26 from the Clinical Study Report, page 70/860). Since the protocol required the anesthesiologist to increase the inspired concentration of anesthetic for a deep LMA removal, in the context of what was documented in the early terminations, the likely explanation for this unexpected finding is that patients who had a deep LMA removal had greater desflurane exposure, associated with the higher respiratory event rate.

Table 26: Major post-induction respiratory events by LMA removal type

	Desflurane (N = 273)		Isoflurane (N = 91)	
Event	Deep Anesthesia (N = 134)	Awake (N = 139)	Deep Anesthesia (N = 42)	Awake (N = 49)
Any event	20 (15%)	7 (5%)	1 (2%)	2 (4%)
Airway obstruction	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Breath-holding	2 (2%)	2 (1%)	0 (0%)	0 (0%)
Bronchospasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Coughing	6 (5%)	0 (0%)	0 (0%)	1 (2%)
Hiccups	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Laryngospasm	11 (8%)	5 (4%)	0 (0%)	2 (4%)
Secretions	3 (2%)	1 (1%)	0 (0%)	1 (2%)
Non-specific desaturation	4 (3%)	1 (1%)	1 (2%)	0 (0%)

The applicant conducted analyses of other covariates (e.g. mode of ventilation, initial airway type, etc). These analyses did not suggest any further factors associated with respiratory events.

7.1.4 Other Search Strategies

An expected array of concomitant medications was used pre-anesthetic, intraoperatively, and during recovery. These drugs included local anesthetics, benzodiazepines, opioids, non-opioid analgesics, antibiotics, anti-emetics, propofol, and dexamethasone. As shown in Table 18 (reproduced verbatim from the Clinical Study Report, pages 61-2/860), following, the use of concomitant medications was balanced between the treatment arms except for the intraoperative use of dexamethasone and propofol. In reviewing the study documents, it appears that, as a rule, the dexamethasone was used to manage airway complications, not as an anti-emetic.

Table 18: Intraoperative concomitant medications (≥ 5% of subjects)

Medication (WHO ATC/DDD name)	Desflurane (N = 300)	Isoflurane (N = 100)
Propofol	57 (19%)	11 (11%)
Bupivacaine	121 (40%)	42 (42%)
Lidocaine	25 (8%)	6 (6%)
Marcaine With Epinephrine	26 (8%)	4 (4%)
Ondansetron	120 (40%)	36 (36%)
Ketorolac	36 (12%)	14 (14%)
Dexamethasone	32 (11%)	4 (4%)
Opioids	246 (82%)	72 (72%)
B&O Supprettes	*1 (<1%)*	*0 (0%)*
Fentanyl	*178 (59%)*	*51 (51%)*
Hydromorphone	*3 (1%)*	*1 (1%)*
Morphine	*78 (26%)*	*22 (22%)*
Pethidine	*0 (0%)*	*1 (1%)*
Paracetamol	37 (12%)	13 (13%)
Cefazolin	80 (27%)	23 (23%)

Source: Statistical Summary Table 19.2

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Patients were hospitalized for the duration of the study, generally under well monitored and supervised conditions and were observed for adverse events. A "How do you feel?" prompt was not required per protocol. Data collection for adverse events began with the induction of anesthesia and continued until 24 hours following the end of study drug or hospital discharge, whichever occurred first.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using both COSTART and MeDRA. The applicant's coding was reasonably accurate.

7.1.5.3 Incidence of common adverse events

The incidence of adverse events in both cohorts was 56% in the desflurane arm and 51% in the isoflurane arm. This reviewer confirmed data in the applicant's table for vomiting, agitation, and "anesthetic complication, neurological" (which was emergence delirium).

7.1.5.4 Common adverse event table (excludes respiratory events)

This reviewer used data from Statistical Summary Table 25.4 (Volume 4, pages 13-17) to generate the following table of the most common adverse events in both cohorts. The common adverse event rates were comparable between treatment groups.

Table 12: Common adverse events (occuring at a rate >1%)

Preferred Term	Desflurane		Isoflurane	
	N	%	N	%
Any AE	**168**	**56.0**	**51**	**51.0**
Pain	118	39.3	40	40.0
Vomiting	35	11.7	12	12.0
Nausea	25	8.3	7	7.0
Agitation	13	4.3	1	1.0
Crying	3	3.0	0	0.0
Eye hemorrhage	7	2.3	2	2.0
Anesthetic complication neurological	6	2.3	0	0.0
Pyresia	3	2.0	0	0.0
Headache	6	2.0	0	0.0
Restlessness	2	2.0	1	1.0
Tachycardia	5	1.7	0	0.0
Chills	5	1.7	1	1.0
Hypothermia	4	1.3	0	0.0

7.1.7 Laboratory Findings

Laboratory tests were not required by the protocol.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure, heart rate, oxygen saturation were documented in the holding area, prior to the start of study drug, every 15 minutes intraoperatively, at the end of study drug administration, and every 5 minutes during emergence.

The applicant provided figures depicting the mean changes from baseline for vital signs. No clinically significant differences were noted between treatment arms.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not required by the protocol and were not performed.

7.1.17 Postmarketing Experience

This reviewer conducted a cursory review of the Adverse Event Reporting System (AERS) database under the search term of "desflurane." Since 1993, AERS has 303 cases that have been reported, of which 240 indicate that SUPRANE (desflurane) is the suspect medication. This reviewer noted several highly medically significant events that do not appear in the current package insert including: hepatic necrosis, ventricular tachycardia ("tachycardia" appears in the labeling), ventricular fibrillation, and cardiac arrest. Some of these cases were reported in the pediatric population.

This reviewer notes that, in August 2006, the Division approved a Changes Being Effected labeling supplement for SUPRANE. The following changes were made to the package insert.

- WARNINGS had language regarding perioperative hyperkalemia resulting in arryhthmias and death and malignant hyperthermia added.
- PRECAUTIONS had language regarding sensitivity hepatitis added.
- ADVERSE REACTIONS had language regarding hepatic failure and hepatic necrosis added.

These changes appear to cover the spectrum of findings in my review of the AERS database.

7.2 Adequacy of Patient Exposure and Safety Assessments

The applicant complied with the requirements of the Pediatric Written Request which required at least 300 patients to be treated with desflurane. Given that desflurane has been approved since 1992, the safety assessments were appropriate and adequate to characterize the adverse event profile in this particular setting.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The study enrolled a total of 400 children aged 2-16 who required general anesthesia for surgery. As detailed in the description of the study results in the Appendix, there was a preponderance of patients in the youngest age stratum (2-6 years old). However, since the Division's prime concern was for the youngest children, this imbalance in the age distribution was desirable.

7.2.1.1 Study type and design/patient enumeration

This was a randomized, single-blind, parallel group, active-controlled clinical trial. The Agency initially requested a double-blind design. However, due to technical issues, the applicant was

permitted to conduct the study single-blind (patient blinded). This reviewer recognizes that the lack of investigator blinding could have biased the results.

7.2.1.2 Demographics

This study enrolled male and female children aged 2 to 16 years. There was a male preponderance (70.7% male, 29.3% female) which is expected for surgical patients in this age group. Of the three age strata (2-6 years old; 7-11 years old; and 12-16 years old), the youngest age strata had the plurality of the patients (50%, 27%, and 23%, respectively).

7.2.1.3 Extent of exposure (dose/duration)

For all patients, the mean duration of the maintenance phase was 49 minutes with a minimum of 4 minutes and a maximum of 217 minutes. As noted in section Section 7.1.3.3 (Table 10), exposures to isoflurane (as a fraction of MAC) were higher than for desflurane.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.2 Postmarketing experience

See Section 7.1.17.

7.2.2.3 Literature

The ten journal articles submitted by the applicant were briefly reviewed.

7.2.3 Adequacy of Overall Clinical Experience

The applicant met the requirements of the Pediatric Written Request (300 patients exposed to desflurane) which was intended to address the "Rule of 3." Therefore, the data obtained are predicted to detect adverse events occurring at an incidence of 1% which is adequate to augment the labeling of this approved drug.

7.2.8 Assessment of Quality and Completeness of Data

Pending any changes to the preliminary report from the Division of Scientific Investigations, the data were of sufficient quality and completeness to complete this review.

7.2.9 Additional Submissions, Including Safety Update

Following the initial submission, the applicant supplied financial disclosure, the SAS transport files, and some clarifying information regarding whether data were imputed.

7.4.2 Explorations for Predictive Factors

The applicant and this reviewer conducted exploratory analyses of cofactors such as mode of ventilation, LMA or facemask, removal of LMA while awake or deep, etc. The major finding in this analysis was that the incidence of respiratory events was higher when the concentration of desflurane was being increased (for deep LMA removal).

7.4.2.3 Explorations for drug-demographic interactions

The applicant analyzed the rates of respiratory events by age and found that the youngest age stratum (2-6 years old) had a disproportionately high incidents of such events.

7.4.3 Causality Determination

In almost all cases, the investigator opined that the major respiratory events were probably associated with the use of desflurane.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Because of the excess toxicity noted in this study, the package insert for SUPRANE will require modification. The indications section is acceptable since it limits the use to maintenance anesthesia in intubated children. Language regarding the respiratory events will be added to the WARNINGS section to inform anesthesiologists of the risks of the use of this drug in non-intubated children.

8.2 Drug-Drug Interactions

The approved label indicates that no clinically significant adverse interactions with commonly used preanesthestic drugs or those used during anesthesia were reported during clinical trials. Benzodiazepines are known to decrease the MAC of desflurane and the ED_{95} of neuromuscular blocking agents.

8.3 Special Populations

According to the approved package insert, no differences were observed in small trials of patients with renal and hepatic insufficiency.

9 OVERALL ASSESSMENT

9.1 Conclusions

Compared to isoflurane, in non-intubated children, desflurane is associated with a marked increase in respiratory events, in particular laryngospasm. The incidence of respiratory events was highest in the youngest subset of children (aged 2-6). The respiratory events appeared to be correlated with increases in the inspired concentration of desflurane.

Because of this, the use of desflurane in non-intubated children should be strongly discouraged. The applicant proposed language in the PRECAUTIONS section of the package insert. In this reviewer's opinion, the appropriate place for such information is in the WARNINGS section.

9.2 Recommendation on Regulatory Action

At the time of writing of this review, labeling negotiations have not been initiated with the applicant. Assuming that acceptable labeling is negotiated, this labeling supplement should be approved.

9.4 Labeling Review

Please see Appendix.

9.5 Comments to Applicant

None.

10 APPENDIX

10.1 Review of Individual Study Reports

This supplement is supported by a single clinical study, protocol 32,363-002.

Title: Comparison of Desflurane and Isoflurane for Face Mask or Laryngeal Mask Airway Anesthesia during Pediatric Surgery

Primary Objective: To assess the safety of desflurane in pediatric patients by determining the incidence of major respiratory events during desflurane anesthesia in non-intubated children and adolescents.

Secondary Objectives: To compare the incidences of major and minor respiratory events during desflurane and isoflurane anesthesia, to compare the recovery characteristics following desflurane and isoflurane anesthesia, to assess the safety and tolerability of desflurane by assessing the hemodynamic and respiratory profile, incidences of adverse events, and requirements for concomitant medication during and after anesthesia.

Study Design: Multicenter, Randomized, Single-Blind (patient is blinded), Active-Controlled, Parallel-Group

Duration: The surgery that the child was to undergo was to be anticipated to last 30 to 120 minutes.

Sample Size: The protocol planned to enroll a total of 400 patients (300 desflurane and 100 isoflurane)

Inclusion Criteria: Patients were to have met all of the following criteria:

1. Children aged 2 to 16 years.
2. American Society of Anesthesiologists physical status of P1, P2, or P3.
3. Patient planned for an elective surgery anticipated to be 30 to 120 minutes in duration.
4. The anesthesia for the surgery was planned to be managed by facemask or LMA during the maintenance phase of anesthesia.
5. Informed consent and assent obtained.

Exclusion Criteria: Patients were not eligible if any of the following criteria were present:

1. Reactive airway disease that had required any form of non-maintenance therapy to treat an acute exacerbation within the past two weeks or required hospital admission within the

past year. If the patient were on stable maintenance therapy for two weeks prior to surgery, this was acceptable.
2. Wheezing on the day of surgery.
3. Body Mass Index above the 95th percentile for age and gender
4. Surgical procedure is or includes tonsillectomy and/or cleft palate repair.
5. History of or family history of malignant hyperthermia.
6. Pregnancy or lactation
7. Previous treatment under this protocol.
8. Exposure to experimental drug within 30 days or other randomized study within 30 days.

Treatment:

Desflurane or isoflurane: to be initiated at an appropriate dose of inspired concentration, according to the patients hemodynamic response, in 60% nitrous oxide, balance oxygen. The minimum end-tidal concentration should be 0.5 MAC. Patients were to have been randomized in a 3:1 ratio (desflurane:isoflurane).

Anesthetic Procedure:

1. Pre-anesthesia planning. Parameters for the anesthetic procedure were to have been prespecified for the following three parameters:
    a. Facemask versus Laryngeal Mask Airway (LMA)
    b. LMA removal (awake versus deep)
    c. Predominant mode of ventilatory assistance (spontaneous, assisted, or controlled)
2. The pre-anesthestic medication was to have been midazolam (up to 20 mg). The use of anticholinergics was discouraged unless there was a high probability of bradycardia. Glycopyrrolate was to have been prohibited.
3. Regional anesthetic techniques (peripheral nerve block, local infiltration, caudal/epidural were to have been permitted. Clonidine was to have been prohibited.
4. Prophylactic anti-emetics were to have been permitted with the exception of those with sedating side effects.
5. Induction was to have been performed with inhaled sevoflurane or intravenous propofol.
6. When the patient's respiratory pattern indicated sufficient anesthetic depth, an oral airway (for facemask) or LMA (lubricant was to have been free of local anesthestic) was to have been inserted.
7. Modifications to the maintenance anesthesia planned (i.e. facemask vs. LMA, mode of ventilatory assistance, and plan for LMA withdrawal) were only to have been changed for patient safety.

Permitted Concomitant Medications:

- Midazolam, up to 20 mg, was permitted as a preanesthetic medication.
- Local anesthetic agents used for peripheral anesthetic techniques.
- "Other intraoperative analgesics may be administered as indicated. Choice of specific agents and doses are at the discretion of the investigator."

- Prophylactic anti-emetic medications (except those with known sedative side effects)
- Propofol (for induction)

Prohibited Medications:

- Glycopyrrolate
- Clonidine
- Anti-emetic medications with known sedative effects (e.g. diphenhydramine)

Outcome Measures:

Primary Assessment:

This study did not assess efficacy. The objective was to compare the incidence of adverse events, in particular, adverse events related to the respiratory system. To address this goal, the applicant devised the following rating scale (excerpted verbatim from the protocol) which was found acceptable by the Division.

Table 4: Respiratory Events	
Event	**Severity/Definition**
Airway Obstruction	Mild (relieved by repositioning the head) Moderate (relieved by positive pressure ventilation) Severe (causing SpO_2 of <90% for >15 seconds, or requiring tracheal intubation)
Breath-holding (including apnea)	Mild (duration <10 seconds) Moderate (duration ≥10 seconds with SpO_2 ≥90%) Severe (causing SpO_2 of <90% for >15 seconds)
Bronchospasm (not included in Zwass[3])	Mild (scattered wheezing) Moderate (diffuse wheezing) Severe (diffuse wheezing with SpO_2 of <90% for >15 seconds)
Coughing	Mild (fewer than 3 coughs) Moderate (3 or more coughs) Severe (3 or more coughs with SpO_2 of <90% for >15 seconds)
Laryngospasm (must rule out airway obstruction)	Mild (no decrease in SpO_2) Moderate (decrease in SpO_2 <95%) Severe (SpO_2 of <90% for >15 seconds, or succinylcholine required)
Secretions	Mild (not requiring suctioning, or seen on routine suctioning) Severe (copious, compromising ventilation with SpO_2 of <90% for >15 seconds)
Hiccups (from Ashworth and Smith[5])	Mild (duration <3 minutes) Moderate (≥ 3 minutes) Severe (any duration associated with SpO_2 of <90% for >15 seconds)
Hemoglobin-oxygen desaturation due to an undefined cause	SpO_2 of <90% for >15 seconds due to a cause not defined above

Other Safety Assessments:

1. Other adverse events. Patients were to be monitored for 24 hours following the discontinuation of study drug or hospital discharge, whichever happened first. Sustained changes in heart rate or blood pressure >30% above or below baseline were to be considered adverse events.
2. Modified Aldrete scale. Patients were to have been assessed every 5 minutes during emergence until the Aldrete score was 8 or greater. The scale used follows (reproduced verbatim from the protocol).

Table 5: Modified Aldrete Score	
Criterion	**Score**
Activity	
Able to move 4 extremities voluntarily or on command	2
Able to move 2 extremities voluntarily or on command	1
Able to move 0 extremities voluntarily or on command	0
Respiration	
Able to breathe deeply and cough freely	2
Dyspnea or limited breathing	1
Apneic	0
Circulation	
Systolic blood pressure ± 20% of preanesthetic level	2
Systolic blood pressure ± 20-49% of preanesthetic level	1
Systolic blood pressure ± 50% of preanesthetic level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
O_2 Saturation	
Able to maintain SpO_2 >92% on room air	2
Needs O_2 inhalation to maintain SpO_2 >90%	1
SpO_2 <90% even with O_2 supplement	0

Statistical Analysis Plan and Definition of Analyzed Study Populations:

- There was no power calculation since there was no hypothesis testing. Rather, the study size was based upon the requirements of the Pediatric Written Request (at least 300 children in the desflurane cohort and a maximum ratio of 3:1 with isoflurane). Study size stipulated in the Written Request was based upon the "Rule of 3."
- All patients who received study drug were to be included in the analysis.
- The primary endpoint was to be the incidence of major respiratory events in the desflurane group.
- Secondary endpoints were to have been:
    - The incidences of major and minor respiratory events in the desflurane and isoflurane arms
    - The incidences of respiratory events by patient age, mode of airway management, mode of ventilatory assistance, and timing of LMA removal
    - A comparison of recovery characteristics after desflurane or isoflurane anesthesia

  - An assessment of the safety of desflurane anesthesia as assessed by the hemodynamic and respiratory profile, incidence of adverse events, and requirements for concomitant medications
- Descriptive statistics for the parameters of interest were to have been calculated including 95% confidence intervals.
- The incidence of major and minor respiratory events were to have been compared using a Fisher-Exact test.

Protocol Amendment: The protocol was amended on December 19, 2003 which was prior to initiating the study (February 4, 2004). The amendment revised the requirements for study drug accountability, redefined the severity definitions for respiratory secretions, and clarified other sections of the protocol.

RESULTS:

Demographics/Exposure

Patient demographics are summarized in Table A1 below.

Table A1: Patient demographics

Category	Desflurane			Isoflurane		
	Age Group (years)			Age Group (years)		
	2-6	7-11	12-16	2-6	7-11	12-16
Children/group	150 (50%)	81 (27%)	69 (23%)	51 (51%)	27 (27%)	22 (22%)
Mean age (years)	3.5	9.0	13.9	4.1	8.8	13.9
Gender [N (%)]						
Female	38 (25)	81 (27)	19 (28)	22 (43)	9 (33)	7 (32)
Male	112 (75)	59 (73)	50 (72)	29 (57)	18 (67)	15 (68)
Race/ethnicity [N (%)]						
White, non-Hispanic	84 (56)	52 (64)	46 (67)	26 (51)	14 (52)	17 (77)
Black, non-Hispanic	34 (23)	12 (15)	17 (25)	16 (31)	5 (19)	2 (9)
Hispanic	15 (10)	6 (7)	1 (1)	6 (12)	3 (11)	1 (5)
Asian, PI	6 (3)	2 (2)	2 (3)	2 (4)	1 (4)	0 (0)
Unknown	5 (3)	4 (5)	1 (1)	0 (0)	2 (8)	2 (9)
Other	6 (3)	5 (5)	2 (3)	1 (2)	2 (8)	0 (0)

There was a larger proportion of patients in the youngest age stratum. However, the Division's primary intent was understanding the effects of desflurane in the youngest children. Therefore, the imbalance in the age groups is acceptable. There was a male predominance. This was expected in this patient population based on the frequencies of pediatric surgical procedures.

Drop-Outs

Four hundred and ten patients were randomized and 400 received study drug. Reasons for not receiving study drug were not related to safety or efficacy (e.g. surgeon preferred a position that required intubation, surgery cancelled, etc.). Six patients in the desflurane cohort discontinued prematurely due to adverse events (see Respiratory Events, following).

Protocol Violations/Deviations

Protocol violations (noncompliance with inclusion/exclusion criteria) and protocol deviations (noncompliance with other protocol-specified procedures) fell into two basic classes, missing data and procedural deviations.

Table 11 of the Clinical Study Report (CSR) lists groups of deviations and which patients fell into each class. A summary of the classes of deviations and numbers of patients follows (Table A2).

Table A2: Number of patients with protocol violation/deviation

Nature of violation/deviation	Number of desflurane patients with deviation (N=300)	Number of isoflurane patients with deviation (N=100)
Missing Data		
No hemodynamic or respiratory parameter data recorded at one or more time points	35	13
Partial hemodynamic or respiratory parameter data recorded at one or more time points	65	22
Inspired and/or end-tidal anesthetic concentration not recorded at one or more time points	33	9
Modified Aldrete scores not 8 or above for three consecutive readings prior to discontinuing Aldrete scoring	21	7
Modified Aldrete scores not recorded or incompletely recorded at one or more timepoints	83	27
Race/ethnicity not recorded	10	4
Height not recorded	5	1
Procedural Issues		
Nitrous oxide not administered during maintenance	2	2
Study drug administered via facemask prior to insertion of LMA	10	1

Nature of violation/deviation	Number of desflurane patients with deviation (N=300)	Number of isoflurane patients with deviation (N=100)
Anticholinergic administered	3	2
Premedication other than midazolam administered	2	0
Gylcopyrrolate administered	2	2
Antiemetic with sedative side effects administered (diphenhydramine – postoperatively)	3	0
Wrong study drug administered (D administered I; I administered D)	1	1
Patient enrolled despite BMI exceeding 95th percentile	18	2

Because of the large number of patients listed as having missing data, this reviewer examined the pertinent SAS transport files (notably EMERGEN.xpt, HRPARAM.xpt, and HRPARAM1.xpt) and queried the applicant. According to the applicant, with a single exception (estimate of the time of emergence when Aldrete scores were not available), no imputation was done. Therefore, missing data was indicated with the characters "UNK" in the dataset. While each patient noted in Table 11 did have at least one missing value, the missing data were rare, with the vast majority of the required data being present.

Given the large number of individual data points to be collected, this reviewer's review of the datasets supports the applicant's assertion that the missing data is sparse and spotty. There are sufficient data to meet the study objectives.

The other instances of protocol noncompliance were either infrequent, insignificant, and/or occurred in equal proportion in both cohorts. Because of this, in this reviewer's opinion, they did not affect the overall conclusions of the study.

Safety Data

Please see the Integrated Summary of Safety in this review for details.

Respiratory Events

The incidence of major and all (major and non-major) respiratory events was higher in the desflurane-treated cohort than the isoflurane-treated patients.

Deaths

There were no deaths.

Serious Adverse Events

Three serious adverse events (SAEs) occurred while patients were still on study (prior to discharge or 24 hours after the termination of study drug, whichever happened first). The SAEs did not appear to be related to the study drug. However, this reviewer notes that all three of the on-study SAEs occurred in the desflurane group.

One patient experienced a wound dehiscence which required re-operation after discharge. This patient was treated with isoflurane. It appears unlikely that this SAE was related to the anesthetic agent used.

Discontinuations due to Adverse Events

Six patients, all in the desflurane group, terminated early due to respiratory events.

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REFERENCES

[1]Arain SR, Shankar H, Ebert TJ. Desflurane Enhances Reactivity During the Use of the Laryngeal Mask Airway. Anesthesiology. 2005;103:495-9.

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/s/

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Sharon Hertz
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I concur with this review.