

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-478/S-006

APPROVAL LETTER

NDA 20-478/S-006

Abbott Laboratories
D-389, AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

30 MAR 2001

Attention: Michael E. Sliwoski, M.S.
Associate Director, Regulatory Affairs

Dear Mr. Sliwoski:

Please refer to your supplemental new drug application dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultane (sevoflurane).

We acknowledge receipt of your submissions dated March 9 and 20, 2001.

We also refer to your teleconferences with the Agency on March 22 and 30, 2001.

This supplemental new drug application provides for the use of Ultane (sevoflurane) in pediatric patients with congenital heart disease.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-478/S-006." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 872-7441.

Sincerely,

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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FINAL PRINTED LABELING

Note: Figures and tables are not included in this attachment.

ULTANE

Sevoflurane

volatile liquid for inhalation

DESCRIPTION

ULTANE (sevoflurane), volatile liquid for inhalation, a nonflammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anesthetic drug. Sevoflurane is fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether and its structural formula is:

Sevoflurane, Physical Constants are:

Molecular weight 200.05

Boiling point at 760 mm Hg 58.6°C

Specific gravity at 20°C 1.520 - 1.525

Vapor pressure in mm Hg 157 mm Hg at 20°C

197 mm Hg at 25°C

317 mm Hg at 36°C

Distribution Partition Coefficients at 37°C:

Blood/Gas 0.63 - 0.69

Water/Gas 0.36

Olive Oil/Gas 47 - 54

Brain/Gas 1.15

Mean Component/Gas Partition Coefficients at 25°C for Polymers Used Commonly

in Medical Applications:

Conductive rubber 14.0

Butyl rubber 7.7

Polyvinylchloride 17.4

Polyethylene 1.3

Sevoflurane is nonflammable and nonexplosive as defined by the requirements of International Electrotechnical Commission 601-2-13.

Sevoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water. Sevoflurane is stable when stored under normal room lighting conditions according to instructions.

Sevoflurane is chemically stable. No discernible degradation occurs in the presence of strong acids or heat. The only known degradation reaction in the clinical setting is through direct contact with CO₂ absorbents (soda lime and Baralyme®) producing pentafluoroisopropenyl fluoromethyl ether, (PIFE, C₄H₂F₆O), also known as Compound A, and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether, (PMFE, C₅H₆F₆O), also known as Compound B.

The production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (KOH and/or NaOH) forming an alkene (Compound A) from sevoflurane similar to formation of 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) from halothane. Baralyme causes more production of Compound A than does soda lime. Laboratory simulations have shown that the concentration of these degradants is inversely correlated with the fresh gas flow rate (See Figure 1).

Figure 1: Fresh Gas Flow Rate versus Compound A Levels in a Circle Absorber System

Sevoflurane degradation in soda lime has been shown to increase with temperature. Since the reaction of carbon dioxide with absorbents is exothermic, this temperature increase will be determined by quantities of CO₂ absorbed, which in turn will depend on fresh gas flow in the anesthesia circle system, metabolic status of the patient, and ventilation. The relationship of temperature produced by varying levels of CO₂ and Compound A production is illustrated in the following *in vitro* simulation where CO₂ was added to a circle absorber system.

Figure 2: Carbon Dioxide Flow Versus Compound A and Maximum Temperature

Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome-plated brass or copper beryllium.

CLINICAL PHARMACOLOGY

Sevoflurane is an inhalational anesthetic agent for use in induction and maintenance of general anesthesia. Minimum alveolar concentration (MAC) of sevoflurane in oxygen for a 40 year old adult is 2.1%. The MAC of sevoflurane decreases with age (see DOSAGE AND ADMINISTRATION for details).

Compound A

Compound A is produced when sevoflurane interacts with soda lime and Baralyme (See DESCRIPTION). Its concentration in a circle absorber system increases as a function of increasing CO₂ absorbent temperature and composition (Baralyme producing higher levels than soda lime), increased body temperature, and increased minute ventilation, and decreasing fresh gas flow rates. It has been reported that the concentration of Compound A increases significantly with prolonged dehydration of Baralyme. Compound A exposure in patients also has been shown to rise with increased sevoflurane concentrations and duration of anesthesia. In a clinical study in which sevoflurane was administered to patients under low flow conditions for ≈2 hours at flow rates of 1 Liter/minute, Compound A levels were measured in an effort to determine the relationship between MAC hours and Compound A levels produced. The relationship between Compound A levels and sevoflurane exposure are shown in Figure 2a.

Figure 2a: ppm• hr versus MAC• hr at Flow Rate of 1 L/min

Compound A has been shown to be nephrotoxic in rats after exposures that have varied in duration from one to three hours. No histopathologic change was seen at a concentration of up to 270 ppm for one hour. Sporadic single cell necrosis of proximal tubule cells has been reported at a concentration of 114 ppm after a 3-hour exposure to Compound A in rats. The LC₅₀ reported at 1 hour is 1050-1090 ppm (male-female) and, at 3 hours, 350-490 ppm (male-female).

An experiment was performed comparing sevoflurane plus 75 or 100 ppm Compound A with an active control to evaluate the potential nephrotoxicity of Compound A in non-human primates. A single 8-hour exposure of Sevoflurane in the presence of Compound A produced single-cell renal tubular degeneration and single-cell necrosis in cynomolgus monkeys. These changes are consistent with the increased urinary protein, glucose level and enzymic activity noted on days one and three on the clinical pathology evaluation. This nephrotoxicity produced by Compound A is dose and duration of exposure dependent.

At a fresh gas flow rate of 1 L/min, mean maximum concentrations of Compound A in the anesthesia circuit in clinical settings are approximately 20 ppm (0.002%) with soda lime and 30 ppm (0.003%) with Baralyme in adult patients; mean maximum concentrations in pediatric patients with soda lime are about half those found in adults. The highest concentration observed in a single patient with Baralyme was 61 ppm (0.0061%) and 32 ppm (0.0032%) with soda lime. The levels of Compound A at which toxicity occurs in humans is not known.

PHARMACOKINETICS

Uptake and Distribution

Solubility

Because of the low solubility of sevoflurane in blood (blood/gas partition coefficient @ 37°C = 0.63-0.69), a minimal amount of sevoflurane is required to be dissolved in the blood before the alveolar partial pressure is in equilibrium with the arterial partial pressure. Therefore there is a rapid rate of increase in the alveolar (end-tidal) concentration (FA) toward the inspired concentration (FI) during induction.

Induction of Anesthesia

In a study in which seven healthy male volunteers were administered 70% N₂O/30%O₂ for 30 minutes followed by 1.0% sevoflurane and 0.6% isoflurane for another 30 minutes the FA/FI ratio was greater for sevoflurane than isoflurane at all time points. The time for the concentration in the alveoli to reach 50% of the inspired concentration was 4-8 minutes for isoflurane and approximately 1 minute for sevoflurane.

FA/FI data from this study were compared with FA/FI data of other halogenated anesthetic agents from another study. When all data were normalized to isoflurane, the uptake and distribution of sevoflurane was shown to be faster than isoflurane and halothane, but slower than desflurane. The results are depicted in Figure 3.

Recovery from Anesthesia

The low solubility of sevoflurane facilitates rapid elimination via the lungs. The rate of elimination is quantified as the rate of change of the alveolar (end-tidal) concentration following termination of anesthesia (FA), relative to the last alveolar concentration (FaO) measured immediately before discontinuance of the anesthetic. In the healthy volunteer study described above, rate of elimination of sevoflurane was similar compared with desflurane, but faster compared with either halothane or isoflurane. These results are depicted in Figure 4.

Protein Binding

The effects of sevoflurane on the displacement of drugs from serum and tissue proteins have not been investigated. Other fluorinated volatile anesthetics have been shown to displace drugs from serum and tissue proteins *in vitro*. The clinical significance of this is unknown. Clinical studies have shown no untoward effects when sevoflurane is administered to patients taking drugs that are highly bound and have a small volume of distribution (e.g., phenytoin).

Metabolism

Sevoflurane is metabolized by cytochrome P450 2E1, to hexafluoroisopropanol (HFIP) with release of inorganic fluoride and CO₂. Once formed HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. No other metabolic pathways for sevoflurane have been identified. *In vivo* metabolism studies suggest that approximately 5% of the sevoflurane dose may be metabolized.

Cytochrome P450 2E1 is the principal isoform identified for sevoflurane metabolism and this may be induced by chronic exposure to isoniazid and ethanol. This is similar to the metabolism of isoflurane and enflurane and is distinct from that of methoxyflurane which is metabolized via a variety of cytochrome P450 isoforms. The metabolism of sevoflurane is not inducible by barbiturates. As shown in Figure 5, inorganic fluoride concentrations peak within 2 hours of the end of sevoflurane anesthesia and return to baseline concentrations within 48 hours post-anesthesia in the majority of cases (67%). The rapid and extensive pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism.

Figure 5: Serum Inorganic Fluoride Concentrations for Sevoflurane and Other Volatile Anesthetics

Elimination

Up to 3.5% of the sevoflurane dose appears in the urine as inorganic fluoride. Studies on fluoride indicate that up to 50% of fluoride clearance is nonrenal (via fluoride being taken up into bone).

Pharmacokinetics of Fluoride Ion

Fluoride ion concentrations are influenced by the duration of anesthesia, the concentration of sevoflurane administered, and the composition of the anesthetic gas mixture. In studies where anesthesia was maintained purely with sevoflurane for periods ranging from 1 to 6 hours, peak fluoride concentrations ranged between 12 μM and 90 μM . As shown in Figure 6, peak concentrations occur within 2 hours of the end of anesthesia and are less than 25 μM (475 ng/mL) for the majority of the population after 10 hours. The half-life is in the range of 15-23 hours.

It has been reported that following administration of methoxyflurane, serum inorganic fluoride concentrations $>50 \mu\text{M}$ were correlated with the development of vasopressin-resistant, polyuric, renal failure. In clinical trials with sevoflurane, there were no reports of toxicity associated with elevated fluoride ion levels.

Figure 6: Fluoride Ion Concentrations Following Administration of Sevoflurane (mean MAC = 1.27, mean duration = 2.06 hr) Mean Fluoride Ion Concentrations (n = 48)

Fluoride Concentrations After Repeat Exposure and in Special Populations

Fluoride concentrations have been measured after single, extended, and repeat exposure to sevoflurane in normal surgical and special patient populations, and pharmacokinetic parameters were determined.

Compared with healthy individuals, the fluoride ion half-life was prolonged in patients with renal impairment, but not in the elderly. A study in 8 patients with hepatic impairment suggests a slight prolongation of the half-life. The mean half-life in patients with renal impairment averaged approximately 33 hours (range 21-61 hours) as compared to a mean of approximately 21 hours (range 10-48 hours) in normal healthy individuals. The mean half-life in the elderly (greater than 65 years) approximated 24 hours (range 18-72 hours). The mean half-life in individuals with hepatic impairment was 23 hours (range 16-47 hours). Mean maximal fluoride values (C_{max}) determined in individual studies of special populations are displayed below.

Table 1: Fluoride Ion Estimates in Special Populations Following Administration of Sevoflurane

PHARMACODYNAMICS

Changes in the depth of sevoflurane anesthesia rapidly follow changes in the inspired concentration.

In the sevoflurane clinical program, the following recovery variables were evaluated:

1. Time to events measured from the end of study drug:

- Time to removal of the endotracheal tube (extubation time)
- Time required for the patient to open his/her eyes on verbal command (emergence time)
- Time to respond to simple command (e.g., squeeze my hand) or demonstrates purposeful movement (response to command time, orientation time)

2. Recovery of cognitive function and motor coordination was evaluated based on:

- psychomotor performance tests (Digit Symbol Substitution Test [DSST], Treiger Dot Test)
- the results of subjective (Visual Analog Scale [VAS]) and objective (objective pain-discomfort scale [OPDS]) measurements
- time to administration of the first post-anesthesia analgesic medication
- assessments of post-anesthesia patient status

3. Other recovery times were:

- time to achieve an Aldrete Score of =8
- time required for the patient to be eligible for discharge from the recovery area, per standard criteria at site
- time when the patient was eligible for discharge from the hospital
- time when the patient was able to sit up or stand without dizziness

Some of these variables are summarized as follows:

Table 2: Induction and Recovery Variables for Evaluable Pediatric Patients in Two Comparative Studies: Sevoflurane versus Halothane

Table 3: Recovery Variables for Evaluable Adult Patients in Two Comparative Studies: Sevoflurane versus Isoflurane

Table 4: Meta-Analyses for Induction and Emergence Variables for Evaluable Adult Patients in Comparative Studies: Sevoflurane versus Propofol

Cardiovascular Effects

Sevoflurane was studied in 14 healthy volunteers (18-35 years old) comparing sevoflurane-O₂ (Sevo/O₂) to sevoflurane-N₂O/O₂ (Sevo/N₂O/O₂) during 7 hours of anesthesia. During controlled ventilation, hemodynamic parameters measured are shown in Figures 7-10:

Figure 7: Heart Rate

Figure 8: Mean Arterial Pressure

Figure 9: Systemic Vascular Resistance

Figure 10: Cardiac Index

Sevoflurane is a dose-related cardiac depressant. Sevoflurane does not produce increases in heart rate at doses less than 2 MAC.

A study investigating the epinephrine induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patients undergoing transsphenoidal hypophysectomy demonstrated that the threshold dose of epinephrine (i.e., the dose at which the first sign of arrhythmia was observed) producing multiple ventricular arrhythmias was 5

mcg/kg with both sevoflurane and isoflurane. Consequently, the interaction of sevoflurane with epinephrine appears to be equal to that seen with isoflurane.

Clinical Trials

Sevoflurane was administered to a total of 3185 patients prior to sevoflurane NDA submission. The types of patients are summarized as follows:

Table 5: Patients Receiving Sevoflurane in Clinical Trials Type of Patients Number Studied

ADULT 2223

Cesarean Delivery 29

Cardiovascular and patients at risk of myocardial ischemia 246

Neurosurgical 22

Hepatic impairment 8

Renal impairment 35

PEDIATRIC 962

Clinical experience with these patients is described below.

Adult Anesthesia

The efficacy of sevoflurane in comparison to isoflurane, enflurane, and propofol was investigated in 3 outpatient and 25 inpatient studies involving 3591 adult patients. Sevoflurane was found to be comparable to isoflurane, enflurane, and propofol for the maintenance of anesthesia in adult patients. Patients administered sevoflurane showed shorter times (statistically significant) to some recovery events (extubation, response to command, and orientation) than patients who received isoflurane or propofol.

Mask Induction

Sevoflurane has a nonpungent odor and does not cause respiratory irritability. Sevoflurane is suitable for mask induction in adults. In 196 patients, mask induction was smooth and rapid, with complications occurring with the following frequencies: cough, 6%; breathholding, 6%; agitation, 6%; laryngospasm, 5%.

Ambulatory Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N₂O in two studies involving 786 adult (18-84 years of age) ASA Class I, II, or III patients. Shorter times to emergence and response to commands (statistically significant) were observed with sevoflurane compared to isoflurane and propofol.

Table 6: Recovery Parameters in Two Outpatient Surgery Studies:

Least Squares Mean ± SEM

Sevoflurane/N₂O Isoflurane/N₂O Sevoflurane/N₂O Propofol/N₂O

Inpatient Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N₂O in two multicenter studies involving 741 adult ASA Class I, II or III (18-92 years of age) patients. Shorter times to emergence, command response, and first post-anesthesia analgesia (statistically significant) were observed with sevoflurane compared to isoflurane and propofol.

Table 7: Recovery Parameters in Two Inpatient Surgery Studies:

Least Squares Mean ± SEM

Sevoflurane/N₂O Isoflurane/N₂O Sevoflurane/N₂O Propofol/N₂O

Pediatric Anesthesia

The concentration of sevoflurane required for maintenance of general anesthesia is age-dependent (see DOSAGE AND ADMINISTRATION). Sevoflurane or halothane was used to anesthetize 1620 pediatric patients aged 1 day to 18 years, and ASA physical status I or II (948 sevoflurane, 672 halothane). In one study involving 90 infants and children, there were no clinically significant decreases in heart rate compared to awake values at 1 MAC. Systolic blood pressure decreased 15-20% in comparison to awake values following administration of 1 MAC sevoflurane; however, clinically significant hypotension requiring immediate intervention did not occur. Overall incidences of bradycardia [more than 20 beats/min lower than normal (80 beats/min)] in comparative

studies was 3% for sevoflurane and 7% for halothane. Patients who received sevoflurane had slightly faster emergence times (12 vs. 19 minutes), and a higher incidence of post-anesthesia agitation (14% vs. 10%).

1 Safety and Efficacy of Sevoflurane Anesthesia in Infants and Children with Congenital Heart Disease (SEVO-96-412).

Sevoflurane (n=91) was compared to halothane (n=89) in a single-center study for elective repair or palliation of congenital heart disease in 180 pediatric patients. The patients ranged in age from 9 days to 11.8 years with an ASA physical status of II, III, and IV (18%, 68%, and 13% respectively). Patients treated with sevoflurane had statistically significantly fewer incidences of moderate bradycardia (p=0.014), fewer recurrent incidences of junctional dysrhythmia (p=0.015), fewer recurrent incidences of moderate arterial desaturation (p=0.050) and fewer recurrent episodes of hypotension requiring treatment with phenylephrine, epinephrine or ephedrine (p=0.013). The overall requirement for phenylephrine, epinephrine, ephedrine or atropine was statistically significantly lower for patients treated with sevoflurane (p=0.018). No other statistically significant differences were observed between treatment groups.

Sevoflurane (n=91) was compared to halothane (n=89) in a single-center study for elective repair or palliation of congenital heart disease. The patients ranged in age from 9 days to 11.8 years with an ASA physical status of II, III, and IV (18%, 68%, and 13% respectively). No significant differences were demonstrated between treatment groups with respect to the primary outcome measures: cardiovascular decompensation and severe arterial desaturation. Adverse event data was limited to the study outcome variables collected during surgery and before institution of cardiopulmonary bypass.

Mask Induction

Sevoflurane has a nonpungent odor and is suitable for mask induction in pediatric patients. In controlled pediatric studies in which mask induction was performed, the incidence of induction events is shown below (see ADVERSE REACTIONS: Possibly/Probably Causally Related).

Table 8: Incidence of Pediatric Induction Events

Sevoflurane (n=836) Halothane (n=660)

Agitation 14% 11%

Cough 6% 10%

Breathholding 5% 6%

Secretions 3% 3%

Laryngospasm 2% 2%

Bronchospasm <1% 0%

n = number of patients.

Ambulatory Surgery

Sevoflurane (n=518) was compared to halothane (n=382) for the maintenance of anesthesia in pediatric outpatients. All patients received N2O and many received fentanyl, midazolam, bupivacaine, or lidocaine. The time to eligibility for discharge from post-anesthesia care units was similar between agents (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

Cardiovascular Surgery

Coronary Artery Bypass Graft (CABG) Surgery

Sevoflurane was compared to isoflurane as an adjunct with opioids in a multicenter study of 273 patients undergoing CABG surgery. Anesthesia was induced with midazolam (0.1-0.3 mg/kg); vecuronium (0.1-0.2 mg/kg), and fentanyl (5-15 mcg/kg). Both isoflurane and sevoflurane were administered at loss of consciousness in doses of 1.0 MAC and titrated until the beginning of cardiopulmonary bypass to a maximum of 2.0 MAC. The total dose of fentanyl did not exceed 25 mcg/kg. The average MAC dose was 0.49 for sevoflurane and 0.53 for isoflurane. There were no significant differences in hemodynamics, cardioactive drug use, or ischemia incidence between the two groups. Outcome was also equivalent. In this small multicenter study, sevoflurane appears to be as effective and as safe as isoflurane for supplementation of opioid anesthesia for coronary bypass grafting.

Non-Cardiac Surgery Patients at Risk for Myocardial Ischemia

Sevoflurane-N2O was compared to isoflurane-N2O for maintenance of anesthesia in a multicenter study in 214 patients, age 40-87 years who were at mild-to-moderate risk for myocardial ischemia and were undergoing elective non-cardiac surgery. Forty-six percent (46%) of the operations were cardiovascular, with the remainder evenly divided between gastrointestinal and musculoskeletal and small numbers of other surgical procedures. The average duration of surgery was less than 2 hours. Anesthesia induction usually was performed with

thiopental (2-5 mg/kg) and fentanyl (1-5 mcg/kg). Vecuronium (0.1-0.2 mg/kg) was also administered to facilitate intubation, muscle relaxation or immobility during surgery. The average MAC dose was 0.49 for both anesthetics. There was no significant difference between the anesthetic regimens for intraoperative hemodynamics, cardioactive drug use, or ischemic incidents, although only 83 patients in the sevoflurane group and 85 patients in the isoflurane group were successfully monitored for ischemia. The outcome was also equivalent in terms of adverse events, death, and postoperative myocardial infarction. Within the limits of this small multicenter study in patients at mild-to-moderate risk for myocardial ischemia, sevoflurane was a satisfactory equivalent to isoflurane in providing supplemental inhalation anesthesia to intravenous drugs.

Cesarean Section

Sevoflurane (n=29) was compared to isoflurane (n=27) in ASA Class I or II patients for the maintenance of anesthesia during cesarean section. Newborn evaluations and recovery events were recorded. With both anesthetics, Apgar scores averaged 8 and 9 at 1 and 5 minutes, respectively.

Use of sevoflurane as part of general anesthesia for elective cesarean section produced no untoward effects in mother or neonate. Sevoflurane and isoflurane demonstrated equivalent recovery characteristics. There was no difference between sevoflurane and isoflurane with regard to the effect on the newborn, as assessed by Apgar Score and Neurological and Adaptive Capacity Score (average=29.5). The safety of sevoflurane in labor and vaginal delivery has not been evaluated.

Neurosurgery

Three studies compared sevoflurane to isoflurane for maintenance of anesthesia during neurosurgical procedures. In a study of 20 patients, there was no difference between sevoflurane and isoflurane with regard to recovery from anesthesia. In 2 studies, a total of 22 patients with intracranial pressure (ICP) monitors received either sevoflurane or isoflurane. There was no difference between sevoflurane and isoflurane with regard to ICP response to inhalation of 0.5, 1.0, and 1.5 MAC inspired concentrations of volatile agent during N₂O-O₂-fentanyl anesthesia. During progressive hyperventilation from PaCO₂ = 40 to PaCO₂ = 30, ICP response to hypocarbia was preserved with sevoflurane at both 0.5 and 1.0 MAC concentrations. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing maneuvers such as hyperventilation.

Hepatic Impairment

A multicenter study (2 sites) compared the safety of sevoflurane and isoflurane in 16 patients with mild-to-moderate hepatic impairment utilizing the lidocaine MEGX assay for assessment of hepatocellular function. All patients received intravenous propofol (1-3 mg/kg) or thiopental (2-7 mg/kg) for induction and succinylcholine, vecuronium, or atracurium for intubation. Sevoflurane or isoflurane was administered in either 100% O₂ or up to 70% N₂O/O₂. Neither drug adversely affected hepatic function. No serum inorganic fluoride level exceeded 45 µM/L, but sevoflurane patients had prolonged terminal disposition of fluoride, as evidenced by longer inorganic fluoride half-life than patients with normal hepatic function (23 hours vs. 10-48 hours).

Renal Impairment

Sevoflurane was evaluated in renally impaired patients with baseline serum creatinine >1.5 mg/dL. Fourteen patients who received sevoflurane were compared with 12 patients who received isoflurane. In another study, 21 patients who received sevoflurane were compared with 20 patients who received enflurane. Creatinine levels increased in 7% of patients who received sevoflurane, 8% of patients who received isoflurane, and 10% of patients who received enflurane. Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL) studied, the safety of sevoflurane administration in this group has not yet been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency (see WARNINGS).

INDICATIONS AND USAGE

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

Sevoflurane should be administered only by 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. Since level of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used.

CONTRAINDICATIONS

Sevoflurane can cause malignant hyperthermia. It Sevoflurane should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents nor in or patients with known or suspected susceptibility to malignant hyperthermia.

WARNINGS

Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest that there is a potential for renal injury which is presumed due to Compound A. Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC•hours and at fresh gas flow rates of <2 L/min may be associated with proteinuria and glycosuria.

While a level of Compound A exposure at which clinical nephrotoxicity might be expected to occur has not been established, it is prudent to consider all of the factors leading to Compound A exposure in humans, especially duration of exposure, fresh gas flow rate, and concentration of sevoflurane. During sevoflurane anesthesia the clinician should adjust inspired concentration and fresh gas flow rate to minimize exposure to Compound A. To minimize exposure to Compound A, sevoflurane exposure should not exceed 2 MAC•hours at flow rates of 1 to <2 L/min. Fresh gas flow rates <1 L/min are not recommended.

Because clinical experience in administering sevoflurane to patients with renal insufficiency (creatinine >1.5 mg/dL) is limited, its safety in these patients has not been established.

Sevoflurane may be associated with glycosuria and proteinuria when used for long procedures at low flow rates. The safety of low flow sevoflurane on renal function was evaluated in patients with normal preoperative renal function. One study compared sevoflurane (N=98) to an active control (N=90) administered for =2 hours at a fresh gas flow rate of =1 Liter/minute. Per study defined criteria (Hou et al.) one patient in the sevoflurane group developed elevations of creatinine, in addition to glycosuria and proteinuria. This patient received sevoflurane at fresh gas flow rates of =800 mL/minute. Using these same criteria, there were no patients in the active control group who developed treatment emergent elevations in serum creatinine.

Malignant Hyperthermia

In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. In clinical trials, one case of malignant hyperthermia was reported. In genetically susceptible pigs, sevoflurane induced malignant hyperthermia. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia, and hypovolemia.

Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous dantrolene sodium, and application of supportive therapy. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Sevoflurane may present an increased risk in patients with known sensitivity to volatile halogenated anesthetic agents.

PRECAUTIONS

During the maintenance of anesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Due to sevoflurane's insolubility in blood, these hemodynamic changes may occur more rapidly than with other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of sevoflurane.

Rare cases of seizures have been reported in association with sevoflurane use (see **PRECAUTIONS**; Pediatric Use and **ADVERSE REACTIONS**).

The recovery from general anesthesia should be assessed carefully before a patient is discharged from the post-anesthesia care unit.

Drug Interactions

In clinical trials, no significant adverse reactions occurred with other drugs commonly used in the perioperative period, including: central nervous system depressants, autonomic drugs, skeletal muscle relaxants, anti-infective agents, hormones and synthetic substitutes, blood derivatives, and cardiovascular drugs.

Intravenous Anesthetics:

Sevoflurane administration is compatible with barbiturates, propofol, and other commonly used intravenous anesthetics.

Benzodiazepines and Opioids:

Benzodiazepines and opioids would be expected to decrease the MAC of sevoflurane in the same manner as with other inhalational anesthetics. Sevoflurane administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

Nitrous Oxide:

As with other halogenated volatile anesthetics, the anesthetic requirement for sevoflurane is decreased when administered in combination with nitrous oxide. Using 50% N₂O, the MAC equivalent dose requirement is reduced approximately 50% in adults, and approximately 25% in pediatric patients (see DOSAGE AND ADMINISTRATION).

Neuromuscular Blocking Agents:

As is the case with other volatile anesthetics, sevoflurane increases both the intensity and duration of neuromuscular blockade induced by nondepolarizing muscle relaxants. When used to supplement alfentanil-N₂O anesthesia, sevoflurane and isoflurane equally potentiate neuromuscular block induced with pancuronium, vecuronium or atracurium. Therefore, during sevoflurane anesthesia, the dosage adjustments for these muscle relaxants are similar to those required with isoflurane.

Potential of neuromuscular blocking agents requires equilibration of muscle with delivered partial pressure of sevoflurane. Reduced doses of neuromuscular blocking agents during induction of anesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation.

Among available nondepolarizing agents, only vecuronium, pancuronium and atracurium interactions have been studied during sevoflurane anesthesia. In the absence of specific guidelines:

1. For endotracheal intubation, do not reduce the dose of nondepolarizing muscle relaxants.
2. During maintenance of anesthesia, the required dose of nondepolarizing muscle relaxants is likely to be reduced compared to that during N₂O/opioid anesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

The effect of sevoflurane on the duration of depolarizing neuromuscular blockade induced by succinylcholine has not been studied.

Hepatic Function

Results of evaluations of laboratory parameters (e.g., ALT, AST, alkaline phosphatase, and total bilirubin, etc.), as well as investigator-reported incidence of adverse events relating to liver function, demonstrate that sevoflurane can be administered to patients with normal or mild-to-moderately impaired hepatic function. However, patients with severe hepatic dysfunction were not investigated.

Occasional cases of transient changes in postoperative hepatic function tests were reported with both sevoflurane and reference agents. Sevoflurane was found to be comparable to isoflurane with regard to these changes in hepatic function.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies on carcinogenesis have not been performed for either sevoflurane or Compound A. No mutagenic effect of sevoflurane was noted in the Ames test, mouse micronucleus test, mouse lymphoma mutagenicity assay, human lymphocyte culture assay, mammalian cell transformation assay, 32 P DNA adduct assay, and no chromosomal aberrations were induced in cultured mammalian cells.

Similarly, no mutagenic effect of Compound A was noted in the Ames test, the Chinese hamster chromosomal aberration assay and the *in vivo* mouse micronucleus assay. However, positive responses were observed in the human lymphocyte chromosome aberration assay. These responses were seen only at high concentrations and in the absence of metabolic activation (human S-9).

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 1 MAC (minimum alveolar concentration) without CO₂ absorbent and have revealed no evidence of impaired fertility or harm to the fetus due to sevoflurane at 0.3 MAC, the highest nontoxic dose. Developmental and reproductive toxicity studies of sevoflurane in animals in the presence of strong alkalis (i.e., degradation of sevoflurane and production of Compound A) have not been conducted. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sevoflurane should be used during pregnancy only if clearly needed.

Labor and Delivery: Sevoflurane has been used as part of general anesthesia for elective cesarean section in 29 women. There were no untoward effects in mother or neonate. (See CLINICAL PHARMACOLOGY, Clinical Trials.) The safety of sevoflurane in labor and delivery has not been demonstrated.

Nursing Mothers: The concentrations of sevoflurane in milk are probably of no clinical importance 24 hours after anesthesia. Because of rapid washout, sevoflurane concentrations in milk are predicted to be below those found with many other volatile anesthetics.

Geriatric Use: MAC decreases with increasing age. The average concentration of sevoflurane to achieve MAC in an 80 year old is approximately 50% of that required in a 20 year old.

Pediatric Use: Induction and maintenance of general anesthesia with sevoflurane have been established in controlled clinical trials in pediatric patients aged 1 to 18 years (see CLINICAL TRIALS and ADVERSE REACTIONS). Sevoflurane has a nonpungent odor and is suitable for mask induction in pediatric patients.

The concentration of sevoflurane required for maintenance of general anesthesia is age dependent. When used in combination with nitrous oxide, the MAC equivalent dose of sevoflurane should be reduced in pediatric patients. MAC in premature infants has not been determined. (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION for recommendations in pediatric patients 1 day of age and older).

The use of sevoflurane has been associated with seizures (see PRECAUTIONS and ADVERSE REACTIONS). The majority of these have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgement should be exercised when using sevoflurane in patients who may be at risk for seizures.

ADVERSE REACTIONS

Adverse events are derived from controlled clinical trials conducted in the United States, Canada, and Europe. The reference drugs were isoflurane, enflurane, and propofol in adults and halothane in pediatric patients. The studies were conducted using a variety of premedications, other anesthetics, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Of the 5182 patients enrolled in the clinical trials, 2906 were exposed to sevoflurane, including 118 adults and 507 pediatric patients who underwent mask induction. Each patient was counted once for each type of adverse event. Adverse events reported in patients in clinical trials and considered to be possibly or probably related to sevoflurane are presented within each body system in order of decreasing frequency in the following listings. One case of malignant hyperthermia was reported in pre-registration clinical trials.

Adverse Events During the Induction Period (from onset of anesthesia by mask induction to surgical incision) Incidence >1%

Adult Patients (N = 118)

Cardiovascular: Bradycardia 5%, Hypotension 4%, Tachycardia 2%

Nervous System: Agitation 7%

Respiratory System: Laryngospasm 8%, Airway obstruction 8%, Breathholding 5%, Cough Increased 5%

Pediatric Patients (N = 507)

Cardiovascular: Tachycardia 6%, Hypotension 4%

Nervous System: Agitation 15%

Respiratory System: Breathholding 5%, Cough Increased 5%, Laryngospasm 3%,
Apnea 2%

Digestive System: Increased salivation 2%

**Adverse Events During Maintenance and Emergence Periods, Incidence >1%
(N = 2906)**

Body as a whole: Fever 1%, Shivering 6%, Hypothermia 1%, Movement 1%,
Headache 1%

Cardiovascular: Hypotension 11%, Hypertension 2%, Bradycardia 5%,
Tachycardia 2%

Nervous System: Somnolence 9%, Agitation 9%, Dizziness 4%, Increased
salivation 4%

Digestive System: Nausea 25%, Vomiting 18%

Respiratory System: Cough increased 11%, Breathholding 2%, Laryngospasm 2%

**Adverse Events, All Patients in Clinical Trials (N = 2906), All Anesthetic Periods,
Incidence <1% (reported in 3 or more patients)**

Body as a whole: Asthenia, Pain

Cardiovascular: Arrhythmia, Ventricular Extrasystoles, Supraventricular
Extrasystoles, Complete AV Block, Bigeminy, Hemorrhage, Inverted T Wave,
Atrial Fibrillation, Atrial Arrhythmia, Second Degree AV Block, Syncope,
S-T Depressed

Nervous System: Crying, Nervousness, Confusion, Hypertonia, Dry Mouth,
Insomnia

Respiratory System: Sputum Increased, Apnea, Hypoxia, Wheezing, Bronchospasm,
Hyperventilation, Pharyngitis, Hiccup, Hypoventilation, Dyspnea, Stridor

Metabolism and Nutrition: Increases in LDH, AST, ALT, BUN, Alkaline
Phosphatase, Creatinine, Bilirubinemia, Glycosuria, Fluorosis, Albuminuria,
Hypophosphatemia, Acidosis, Hyperglycemia

Hemic and Lymphatic System: Leucocytosis, Thrombocytopenia

Skin and Special Senses: Amblyopia, Pruritus, Taste Perversion, Rash, Conjunctivitis

Urogenital: Urination Impaired, Urine Abnormality, Urinary Retention, Oliguria

See WARNINGS for information regarding malignant hyperthermia.

Adverse Events During Post-Marketing Experience: As with other anesthetic agents, rare cases of seizure-like activity with spontaneous resolution have been reported when receiving sevoflurane anesthesia. The causal relationship of these cases with sevoflurane has not been established. Post-marketing reports indicate that sevoflurane use has been associated with seizures. The majority of cases were in children and young adults, most of whom had no medical history of seizures. Several cases reported no concomitant medications, and at least one case was confirmed by EEG. Although many cases were single seizures that resolved spontaneously or after treatment, cases of multiple seizures have also been reported. Seizures have occurred during, or soon after sevoflurane induction, during emergence, and during post-operative recovery up to a day following anesthesia. One death has been reported in association with sevoflurane administration and seizures.

Rare cases of malignant hyperthermia have been reported (see CONTRAINDICATIONS and WARNINGS).

Laboratory Findings: Transient elevations in glucose, liver function tests, and white blood cell count may occur as with use of other anesthetic agents.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken: discontinue administration of sevoflurane, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function.

DOSAGE AND ADMINISTRATION

The concentration of sevoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane. The administration of general anesthesia must be individualized based on the patient's response.

Pre-anesthetic Medication: No specific premedication is either indicated or contraindicated with sevoflurane. The decision as to whether or not to premedicate and the choice of premedication is left to the discretion of the anesthesiologist.

Induction: Sevoflurane has a nonpungent odor and does not cause respiratory irritability; it is suitable for mask induction in pediatrics and adults.

Maintenance: Surgical levels of anesthesia can usually be achieved with concentrations of 0.5 - 3% sevoflurane with or without the concomitant use of nitrous oxide. Sevoflurane can be administered with any type of anesthesia circuit.

**Table 9: MAC Values for Adults and Pediatric Patients According to Age
Age of Patient Sevoflurane Sevoflurane
(years) in Oxygen in 65% N₂O/35% O₂**

HOW SUPPLIED

ULTANE (sevoflurane), Volatile Liquid for Inhalation, is packaged in amber colored bottles containing 250 mL sevoflurane, List 4456, NDC # 0074-4456-02 (glass) and NDC # 0074-4456-04 (plastic).

SAFETY AND HANDLING

Occupational Caution

There is no specific work exposure limit established for sevoflurane. However, the National Institute for Occupational Safety and Health has recommended an 8 hour time-weighted average limit of 2 ppm for halogenated anesthetic agents in general (0.5 ppm when coupled with exposure to N₂O).

STORAGE

Store at controlled room temperature, 15° - 30°C (59° - 86°F).

Manufactured by:

Abbott Laboratories, North Chicago, IL 60064, USA under license from Maruishi
Pharmaceutical Company LTD. 2-3-5, Fushimi-machi, Chuo-Ku, Osaka, Japan.

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ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-478/S-006

MEDICAL REVIEW



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857**

REVIEW AND EVALUATION OF CLINICAL DATA

NDA #: 20-478

Supplement #: SE8-006

Sponsor: Abbott

Generic Name: Sevoflurane

Proprietary Name: Ultane

Pharmacologic Class: Inhalation anesthetic

Purpose: Pediatric Exclusivity

Proposed Indication: General anesthesia in infants and children with congenital heart disease

Submission Date: June 1, 2000

Clinical Reviewer: Nancy Chang, MD

Statistical Reviewer: Stella Grosser, Ph.D.

Completion Date: November 6, 2000

Executive Summary

The current submission is a request for pediatric exclusivity following a Pediatric Written Request by the Agency. The submitted study report is also used to support proposed changes to the label.

Recommendations

Only a limited spectrum of safety and efficacy data was collected in this submission. However, in conjunction with previous data, this study supports the safety and efficacy of sevoflurane used for the induction and maintenance of anesthesia in pediatric patients undergoing elective cardiac surgery.

- A. Pediatric exclusivity has been granted
- B. Changes are recommended in the proposed package insert to balance and clarify the safety claims made by the sponsor.

Summary of clinical findings

Brief overview of clinical program

Ultane (sevoflurane) is an inhalation anesthetic approved for induction and maintenance of general anesthesia in adult and pediatric patients. The current submission is a request for pediatric exclusivity following a Pediatric Written Request by the Agency. It includes one study report of 180 pediatric patients undergoing elective repair or palliation of congenital heart disease under sevoflurane or halothane anesthesia.

Efficacy

Outcome measures relating to efficacy were not significantly different between the sevoflurane and halothane groups. The sponsor does not propose any labeling changes with regard to efficacy.

Safety

180 pediatric patients ages 9 days to 11.8 years were studied while undergoing elective repair or palliation of congenital heart disease under

sevoflurane or halothane anesthesia. Safety information was collected only if defined as a primary or secondary outcome measure. No follow-up was done, and no data were collected during or after cardiopulmonary bypass. Therefore, the spectrum of safety data obtainable from this study is limited in scope. However, the data generally support the safety and efficacy of sevoflurane used for the induction and maintenance of anesthesia in this population.

The data suggest that, compared to halothane, sevoflurane is associated

However, several problems related to study design, execution, and analysis have been identified in this review (discussed in the clinical review below and in the study review in the appendix).

The proposed label changes have been edited in an attempt to take these issues into account, but also to provide information that might be useful to practitioners.

Dosing

No new information was obtained from this study to suggest a change in the current dosing recommendations.

Special Populations

This submission is a request for pediatric exclusivity following a Pediatric Written Request by the Agency. Pediatric exclusivity has already been granted in response to this submission.

Clinical Review

Introduction and Background

A. Indications and state of armamentarium

Ultane (sevoflurane) is a halogenated inhalation anesthetic that is currently labeled for induction and maintenance of general anesthesia in adult and pediatric patients. Like halothane, sevoflurane has low pungency and respiratory irritability and is suitable for mask inhalation induction of anesthesia. Although halothane has traditionally been the inhalational agent of choice for infants and children, it is more soluble in blood than sevoflurane, and it is also thought to cause more myocardial depression and dysrhythmias than sevoflurane. These qualities suggest that sevoflurane might be a safer anesthetic agent in infants and children undergoing cardiac surgery. On the other hand, production of compound A and inorganic fluoride upon degradation and metabolism of sevoflurane suggests that there is a potential for nephrotoxicity with the use of sevoflurane.

B. Product Development

The current submission is a study report made in response to a Pediatric Exclusivity Written Request of March 2, 2000. Exclusivity has been granted, but the sponsor is also requesting labeling changes based on the results of this study.

C. Proposed Labeling

Proposed changes to the package insert include the following claims about sevoflurane-treated patients compared to halothane-treated patients:

Clinically relevant findings from other review disciplines or consults

Production of compound A and inorganic fluoride upon degradation and metabolism of sevoflurane suggests that there is a potential for nephrotoxicity with the use of sevoflurane.

Review Methods

Submission SE8-006 under NDA 20-478 (volumes 1-3, received 6/1/2000) was examined for this review.

Description of data sources

This submission includes the clinical/statistical report for protocol SEVO-96-412, along with tabulated individual subject data, and the original and revised study protocols. Referenced literature is included in an appendix.

Review of Efficacy

The sponsor investigated the following measures related to efficacy: time for anesthetic induction, patient acceptance of induction, agitation during induction, cough, breath-holding, and excessive salivation. None of these outcome measures differed between the sevoflurane and halothane treated groups, and no label claims are being sought relating to these measures.

Integrated Review of Safety

Adequacy of patient exposure and safety assessment

A total of 180 pediatric patients, ages 9 days to 11.8 years, were studied. Patients undergoing elective repair or palliation of congenital heart disease were randomized to receive sevoflurane or halothane for induction and maintenance of anesthesia. Outcome variables were recorded from the time of anesthesia induction until the end of surgery, except in those patients who went on cardiopulmonary bypass (CPB). CPB patients were only observed

until placement of the partial aortic occlusion clamp prior to aortic cannulation. Ninety patients in each group were specified in the Pediatric Written Request from the Agency to provide an 80% chance of detecting a difference between halothane and sevoflurane in the occurrence of severe arterial desaturation or cardiovascular decompensation, using a significance level of 0.05.

Adverse events monitoring was limited to the study outcome variables for the duration of the study. No post-operative follow-up was performed. Therefore, complete safety data is lacking, and no information is known about adverse events outside of the study outcome variables.

Hemodynamics and arterial saturations were collected continuously by computer, and six seconds of lead II were recorded automatically every minute for evaluation of cardiac rhythm. Medications taken during the course of the study were recorded on the appropriate CRF page. A trained observer recorded the remaining primary and secondary safety outcomes.

Methods and specific findings of safety review

Primary safety variables were cardiovascular decompensation (CVD) and severe arterial desaturation (SAD).

CVD was defined as the occurrence of any of the following:

- Severe bradycardia (> 30% decrease in the resting heart rate for > 15 seconds)
- Severe hypotension (> 30% decrease in the resting mean arterial blood pressure for > 15 seconds)
- Electrical cardioversion and defibrillation
- Cardiac massage

SAD was defined as a > 20% decrease in the resting arterial saturation for > 15 seconds.

Secondary outcome variables related to safety, as analyzed in the final study report, were:

1. cough
2. breath holding
3. salivation

4. upper airway obstruction	
5. bronchospasm	
6. moderate hypotension	% pts, #episodes, total duration
7. moderate bradycardia	% pts, #episodes, total duration
tachycardia	% pts, #episodes, total duration
8. junctional dysrhythmia	% pts, #episodes
9. ventricular dysrhythmia	% pts, #episodes
10. overall emergent drug use	% pts
(epinephrine/phenylephrine/ephedrine/atropine)	
11. phenylephrine/epinephrine/ephedrine use	% pts, #episodes
12. atropine	% pts, #episodes
13. moderate arterial desaturation	% pts, #episodes, total duration
14. lactate levels	

The sponsor found no significant differences between groups with respect to the primary outcome measures. As indicated above, the secondary results were split into many subcategories. Therefore, a specific variable might be examined in terms of the percentage of patients experiencing an event; the distribution of patients by number of episodes; and the mean duration of events.

¹ Total duration is the combined total time of all episodes for each patient experiencing one or more events.

Discussion

1. The sponsor collected only a limited spectrum of safety data. However, the outcome measures that were studied were adequately collected as defined.
2. With regard to the outcome measures that were studied, sevoflurane appears to be as safe, or possibly safer, than halothane in this population.
3. Sevoflurane and halothane were not found to be significantly different in regard to the primary outcome measures.
4. Some “significant” differences were found between groups in some secondary outcome measures. However, for every “positive” result showing a safety advantage for sevoflurane, many negative results

occurred, making interpretation of clinical significance somewhat difficult.

5. Some issues of study execution and design also complicate the interpretation of the data (discussed in more detail in the study review in the appendix):
 - Anesthesiologists who made decisions about pressor administration were not blinded to the study drug
 - Enrollment/randomization procedure is somewhat suspect: a patient enrolled in the halothane group was dropped out because the investigator preferred to give sevoflurane
 - A patient with a pacemaker in the sevoflurane group was included in the analyses of hypotension, pressor requirements, and desaturation.
 - Medications that could affect the outcome of primary and secondary variables (e.g. nipride, dopamine, lasix, albumin) were not regulated in the study protocol.

Review of package insert

The sponsor proposes to make the following changes to the **Clinical Trials/Pediatric Anesthesia** section of the existing package insert:

1.

changed to

“Sevoflurane or halothane was used to anesthetize **1620** pediatric patients aged 1 day to 18 years, and ASA physical status I or II (**948** sevoflurane, **672** halothane).

2.

The following section added:

Discussion of proposed changes to the package insert

1. The proposed changes in the numbers of pediatric patients studied are consistent with the submitted study report.
 2. The reported findings that are the bases for the proposed new paragraph raise concerns regarding the validity of analysis and clinical interpretation. This is discussed in more detail in the study review in the Appendix and in the safety review above.
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Suggested revision of this section would be as follows:

Sevoflurane (n=91) was compared to halothane (n=89) in a single-center study for elective repair or palliation of congenital heart disease. The patients ranged in age from 9 days to 11.8 years with an ASA physical status of II, III, and IV (18%, 68%, and 13% respectively).

No significant differences were demonstrated between treatment groups with respect to the primary outcome measures: cardiovascular decompensation and severe arterial desaturation. Adverse event data was limited to the study outcome variables collected during surgery and before institution of cardiopulmonary bypass.”

Conclusions

This was a study of 180 pediatric patients undergoing elective repair or palliation of congenital heart disease under sevoflurane or halothane anesthesia. The study results support the safety and efficacy of sevoflurane used for the induction and maintenance of general anesthesia in this population. In the outcome measures studied, trends are seen favoring sevoflurane as a safer anesthetic. However, the study results that are being used as the basis for labeling changes suffer from problems of study design, execution, and analysis, as discussed in the safety review above and the study review in the appendix.

The proposed labeling changes have been edited to reflect these conclusions.

Appendix

Individual Study Review: Protocol SEVO-96-412

The Safety and Efficacy of Sevoflurane Anesthesia in Infants and Children with Congenital Heart Disease

Financial Disclosure

Financial disclosure forms for all investigators and subinvestigators were reviewed. No significant financial interests (21CFR54.2) were disclosed.

STUDY PLAN

Randomized, prospective, open-label trial. Infants and children less than 12 years of age scheduled for elective repair or palliation of congenital heart disease were randomly allocated to receive halothane or sevoflurane for inhalation induction and maintenance of anesthesia. The anesthesiologists administering the study drugs knew the drug identities; however, a blinded independent observer recorded outcome events.

The design called for a minimum of 180 evaluable patients, with 90 in each study group. Evaluation for outcome measures commenced with induction of anesthesia. The study terminated at the conclusion of surgery, except for patients requiring cardiopulmonary bypass. In these cases, the study terminated with placement of the partial aortic occlusion clamp prior to aortic cannulation.

Following premedication with midazolam (0.5-1 mg/kg po or 0.1-0.2 mg/kg SQ) in patients one year or older, patients were to undergo inhalation induction of anesthesia. Sevoflurane or halothane was to be administered in 3 L/min of nitrous oxide and 2 L/min of oxygen. The initial dose of halothane was to be 0.5%, increased by 0.5% increments every 3 breaths until the onset of rhythmic breathing and loss of the eye lid reflex. The initial sevoflurane dose was to be 1%, increased by 1% increments every 3 breaths. The maximum delivered concentration of halothane was not to exceed 4%, and the maximum sevoflurane concentration was to be 8%. All delivered concentrations and their rate of increase would be decreased by half in patients with congestive heart failure. After induction was complete, the delivered concentration of the volatile agent would be decreased to 1 MAC, an intravenous catheter placed, and 0.1 mg/kg pancuronium would be administered. Thereafter, positive pressure ventilation would be provided via face mask to maintain normocarbida, nitrous oxide would be discontinued, and the oxygen flow rate increased to 5 L/min. Adjustments in the volatile anesthetic concentrations would be made as appropriate for intubation (5 minutes after pancuronium), radial artery catheterization, positioning, and surgery. A 5 mcg/kg bolus of fentanyl would be administered immediately prior to incision, followed by a continuous infusion (5 mcg/kg/hr).

As written, the protocol is in compliance with the current label recommendation that sevoflurane exposure at flow rates of 1 L/minute not exceed 2 MAC-hr. Flow rates specified were all well in excess of 2 L/minute.

Primary outcome variables

- A. Cardiovascular Decompensation (CVD), defined as any of the following occurring during the study period:
1. severe bradycardia: >30% decrease in the resting heart rate for >15 seconds
 2. severe hypotension: >30% decrease in the resting mean arterial pressure for > 15 seconds
 3. electrical cardioversion
 4. defibrillation
 5. cardiac massage
- B. Severe Arterial Desaturation (SAD), defined as >20% decrease in the resting arterial saturation for > 15 seconds

Both primary outcome variables were considered to be safety variables. Although not described in the final study protocol, the statistical methods section of the completed study report states that comparisons of the total number of episodes per patient and the total duration per patient for each condition were to be compared between treatment groups.

The original protocol called for a blinded interim analysis after 90 patients were completed, with plans to terminate the trial if a significant difference was found between the treatment groups in the incidence of CVD or SAD. This interim analysis, conducted after 91 patients were studied, did not show a significant difference between the groups, so the trial was continued. However, the protocol was modified to include a comparison of arterial

blood lactate levels to help determine the clinical significance of any blood pressure differences noted between study groups.

Secondary outcome variables

1. time for anesthetic induction: from initial mask placement until the first attempt at intravenous access
2. patient acceptance of induction: good if no purposeful movements after face mask placement; poor if purposeful movements to remove mask are noted
3. agitation during induction: present if struggling or marked motor activity is noted; absent if no or mild motor activity
4. moderate hypotension: 15-30% decrease in the resting mean arterial blood pressure for >15 seconds
5. moderate bradycardia: 15-30% decrease in the resting heart rate for >15 seconds
6. tachycardia: >20% increase in the resting heart rate for > 15 seconds
7. junctional dysrhythmia: ≥ 3 consecutive beats on any of the 6-second epochs recorded every minute (lead II)
8. ventricular dysrhythmia: ≥ 1 wide QRS on any of the 6-second epochs recorded every minute (lead II)
9. emergent drug use: the use of either phenylephrine or epinephrine for the treatment of hypotension, bradycardia, or cyanosis persisting for more than 15 seconds despite discontinuation of nitrous oxide and decrease of the inspired vapor to 0.33 MAC.
10. cough: 2 or more consecutive during induction
11. breath holding: during induction
12. excess salivation: saliva on face or neck during induction
13. upper airway obstruction: inspiratory retraction/tracheal tugging during induction
14. bronchospasm: airway pressure > 30 cm H₂O or a 50% increase in airway pressure
15. moderate desaturation: 10-20% decrease for > 15 seconds

STUDY OUTCOME

Protocol Deviations

According to the sponsor, "Protocol deviations occurring during the study period were not appropriately documented by the Investigator; however, it was determined that analyses of the primary and secondary outcome variables were not compromised by this omission." The only deviation documented in the submission is that ephedrine was used for severe hypotension by one of the study personnel, although the protocol specified the use of either phenylephrine or epinephrine. Ephedrine use was recorded similarly as phenylephrine/epinephrine use.

An additional discrepancy found on review of the data is in the use of midazolam premedication. The original protocol called for midazolam premedication except in patients less than one year who do not require premedication. Although 49% of patients were aged 1 year or more, only 6 patients (3.3%) received midazolam, four in the halothane group and 2 in the sevoflurane group.

Patient Disposition

A total of 182 patients were enrolled and randomized. Of these, 180 completed the study (91 sevoflurane, 89 halothane), and two were withdrawn prior to treatment. One patient randomized to sevoflurane was withdrawn due to a vaporizer malfunction, and another patient randomized to halothane was withdrawn at the investigator's request. All 180 treated patients were included in the analyses except for one sevoflurane patient who was on a pacemaker prior to enrollment. This patient was excluded from the analyses of bradycardias and dysrhythmias.

Demographics

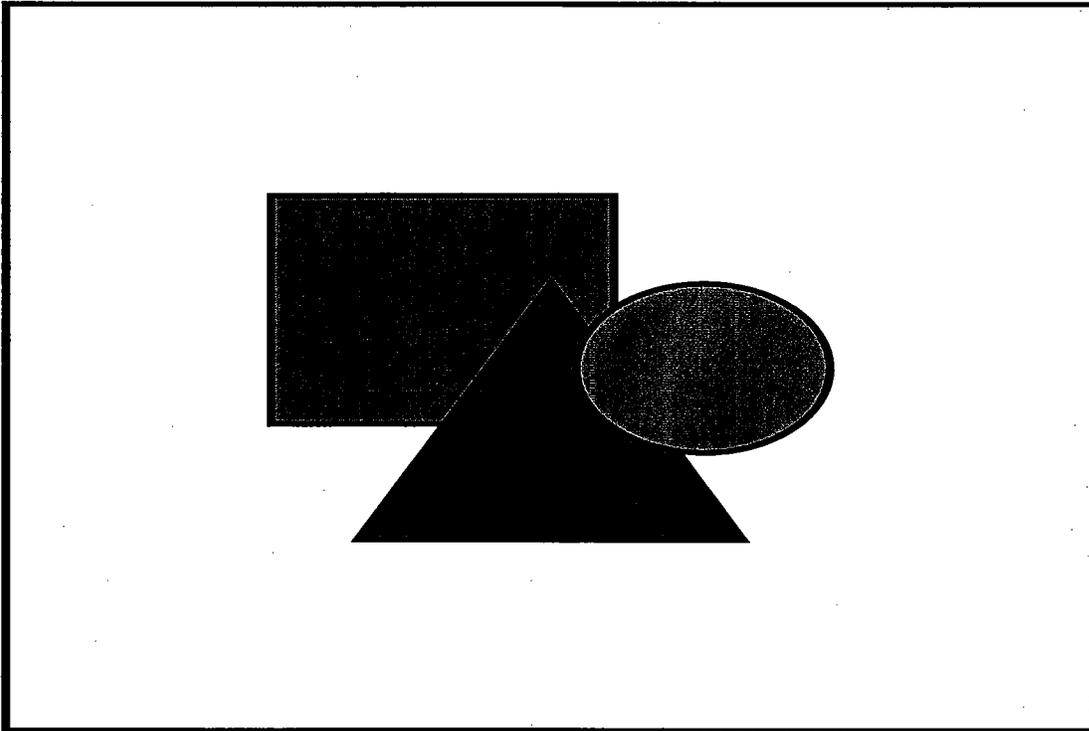
Prior to randomization, patients were separated by age groups of <1 year or > 1 year, then assigned to one of 4 groups according to baseline medical condition: asymptomatic, cyanotic, CHF, or both cyanotic and CHF. Randomization occurred in blocks of ten within each of these 8 groups. As expected, the two treatment groups were very similar in their baseline medical conditions. In addition, there was no significant difference between treatment groups with respect to age, gender, weight, use of premedication, ASA Class, baseline vital signs, and concomitant medical conditions by system.

RESULTS

The treatment groups were similar with respect to the duration of study drug administration, the use of cardiopulmonary bypass during the surgical procedure, the total doses of fentanyl and pancuronium used, and the administration of other medications during the study.

Primary Outcome Variables

No statistical differences ($p \leq 0.05$) were found in the proportions of individual patients experiencing CVD or SAD between treatment groups. In addition, there was no difference between treatment groups in the proportions of patients experiencing any of the event subcategories comprising CVD: severe bradycardia, severe hypotension, fibrillation, cardioversion, and cardiac massage. Primary outcome variables were further assessed by examining the incidence and duration of severe bradycardia, severe hypotension, fibrillation, and severe arterial desaturation. Again, no significant differences were found between the two treatment groups. Sponsor's table follows:



Secondary Outcome Variables

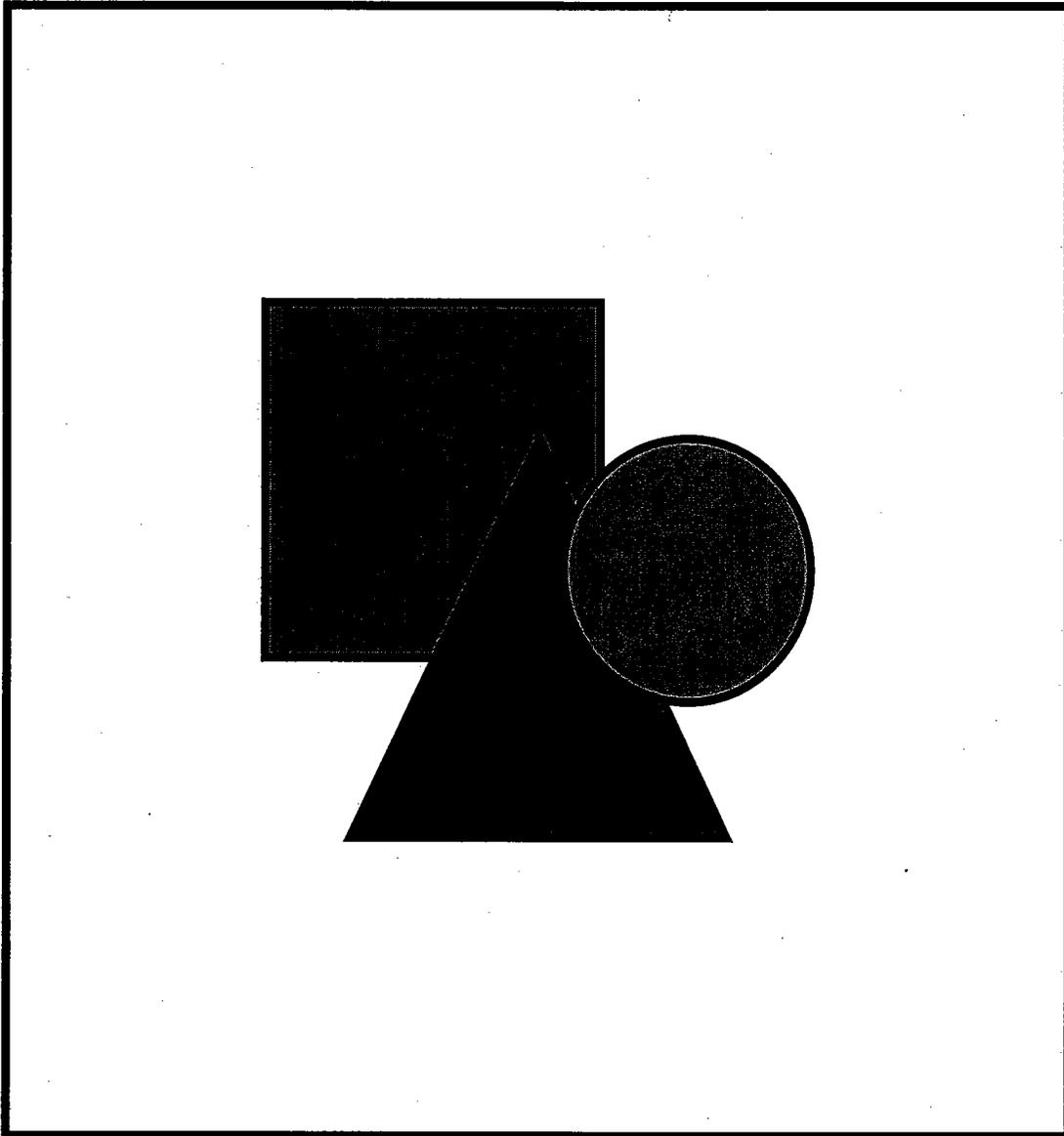
No statistical differences ($p \leq 0.05$) were found between groups with respect to the following secondary outcome variables: time to induction, patient acceptance of induction, agitation during induction, cough, breath holding, salivation, upper airway obstruction, bronchospasm, moderate hypotension, tachycardia, and ventricular dysrhythmia.

Moderate Bradycardia

The total duration of episodes, and the distribution of patients experiencing more than 1 episode of moderate bradycardia were not significantly different between treatment groups. However, the number of patients experiencing moderate bradycardia was found to be different between treatment groups. (Sevoflurane 8 patients (9%), versus Halothane 20 patients (22%), $p=0.014$.)

Total number of episodes was 17 for the Sevoflurane group; 24 for the Halothane group. The mean episode duration was shorter in the halothane group (2.2 minutes halothane; 4.0 minutes sevoflurane).

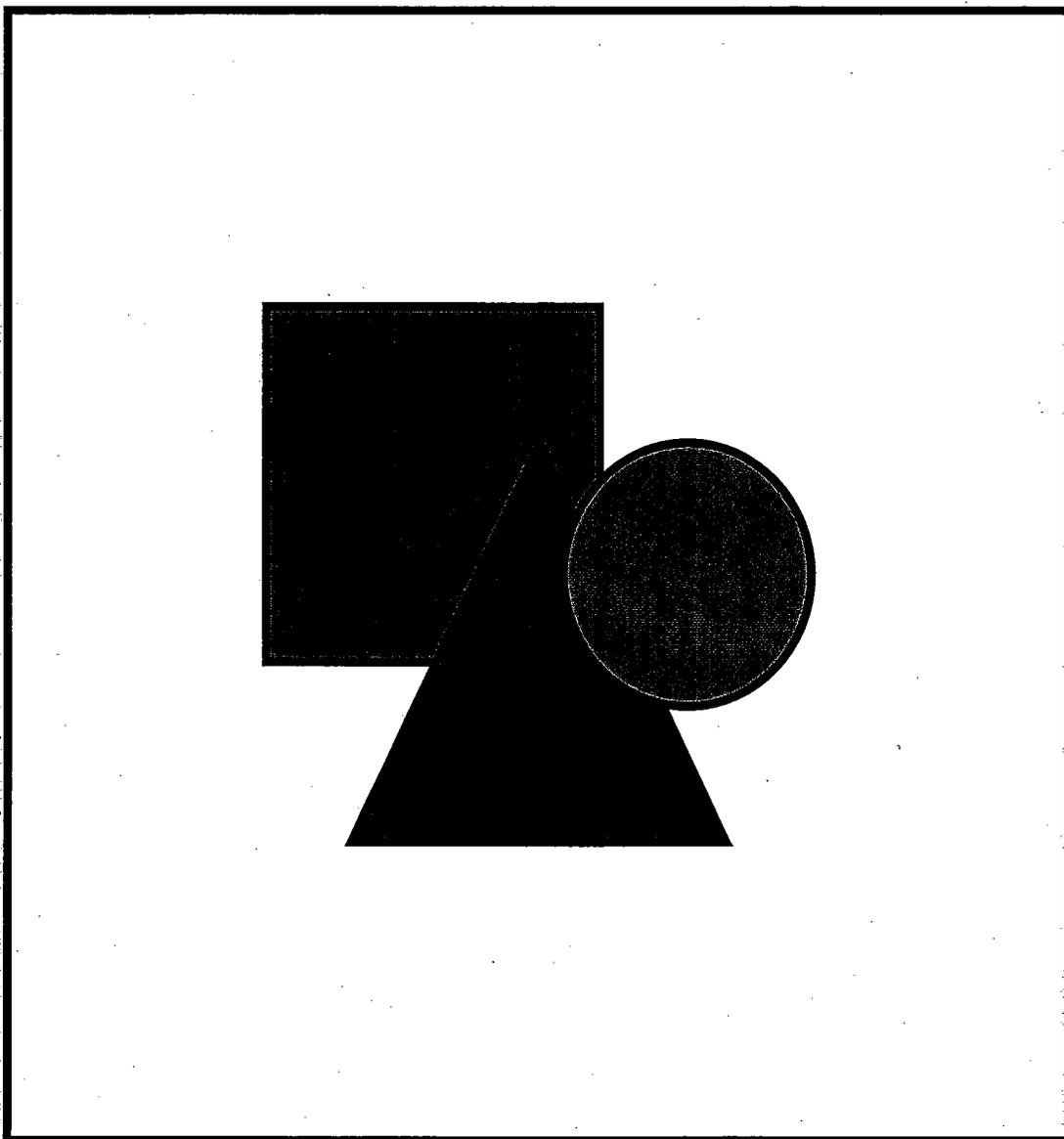
Sponsor's table follows:



Junctional Dysrhythmia

No significant difference was found between the 2 treatment groups in the proportion of patients experiencing junctional dysrhythmia. However, by analyzing the distribution of patients by number of episodes, the sponsors

were able to detect a significant difference between treatment groups in the number of patients experiencing 5 or more episodes of junctional dysrhythmias. (2 in the sevoflurane group versus 13 in the halothane group). Sponsors table follows:



Emergent Drug Use

This secondary outcome measure was defined in the original protocol as the use of either phenylephrine or epinephrine for the treatment of hypotension, bradycardia, or cyanosis persisting for more than 15 seconds despite

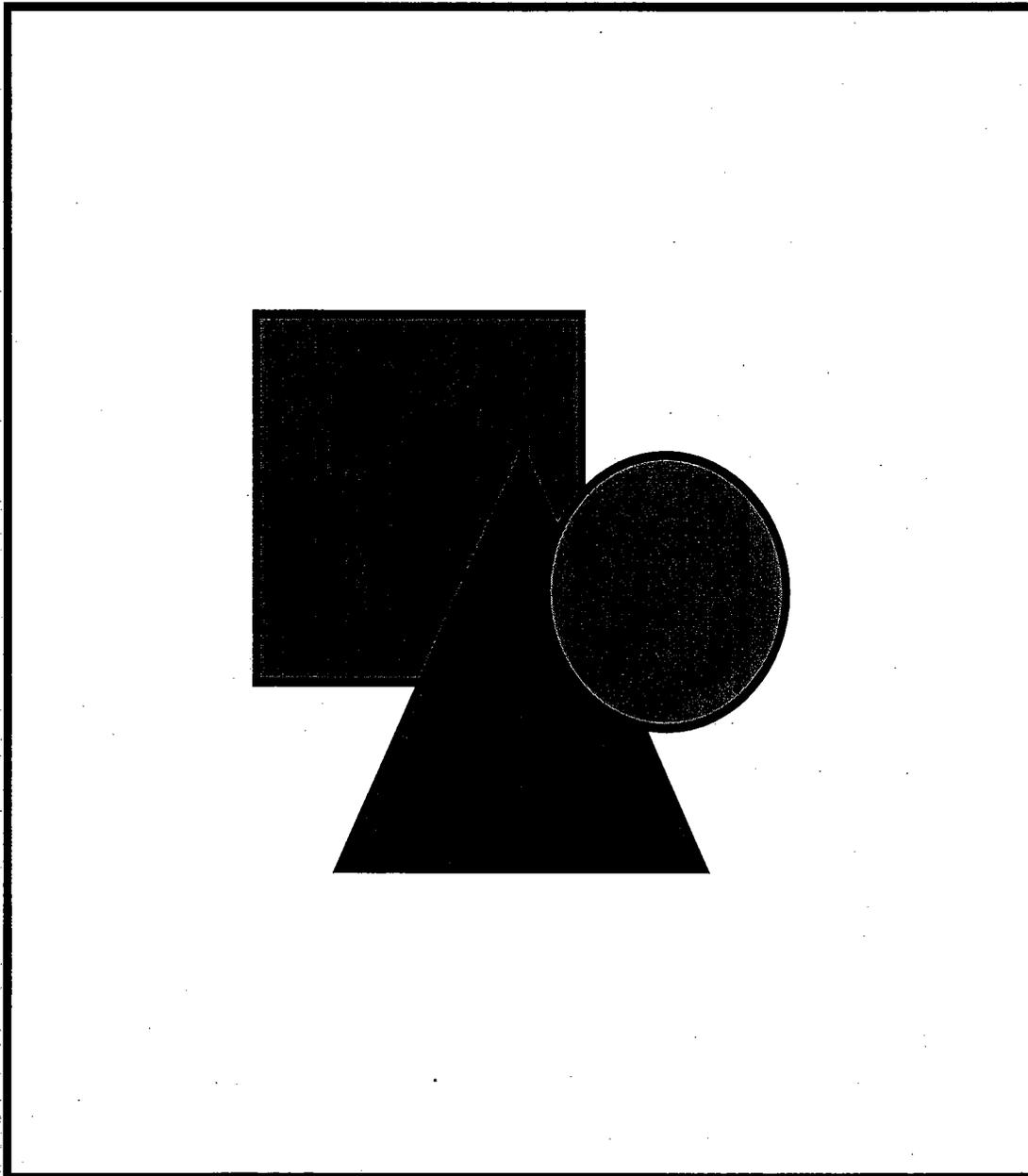
discontinuation of nitrous oxide and decrease of the inspired vapor to 0.33 MAC. However, in the submitted final study report, the analysis considered all of the following items:

1. phenylephrine, epinephrine, or ephedrine use – number of individuals
2. phenylephrine, epinephrine, or ephedrine use – distribution of patients by number of episodes
3. atropine use – number of individuals
4. atropine use – distribution of patients by number of episodes
5. overall emergent drug use – number of individuals requiring phenylephrine, epinephrine, ephedrine, or atropine

Significant differences were found in the following categories:

- a. Number of patients experiencing 2 or more administrations of phenylephrine, epinephrine, or ephedrine (8 halothane patients versus 1 sevoflurane patient)
- b. % of patients requiring phenylephrine, epinephrine, ephedrine or atropine (20% halothane patients versus 8% sevoflurane patients)

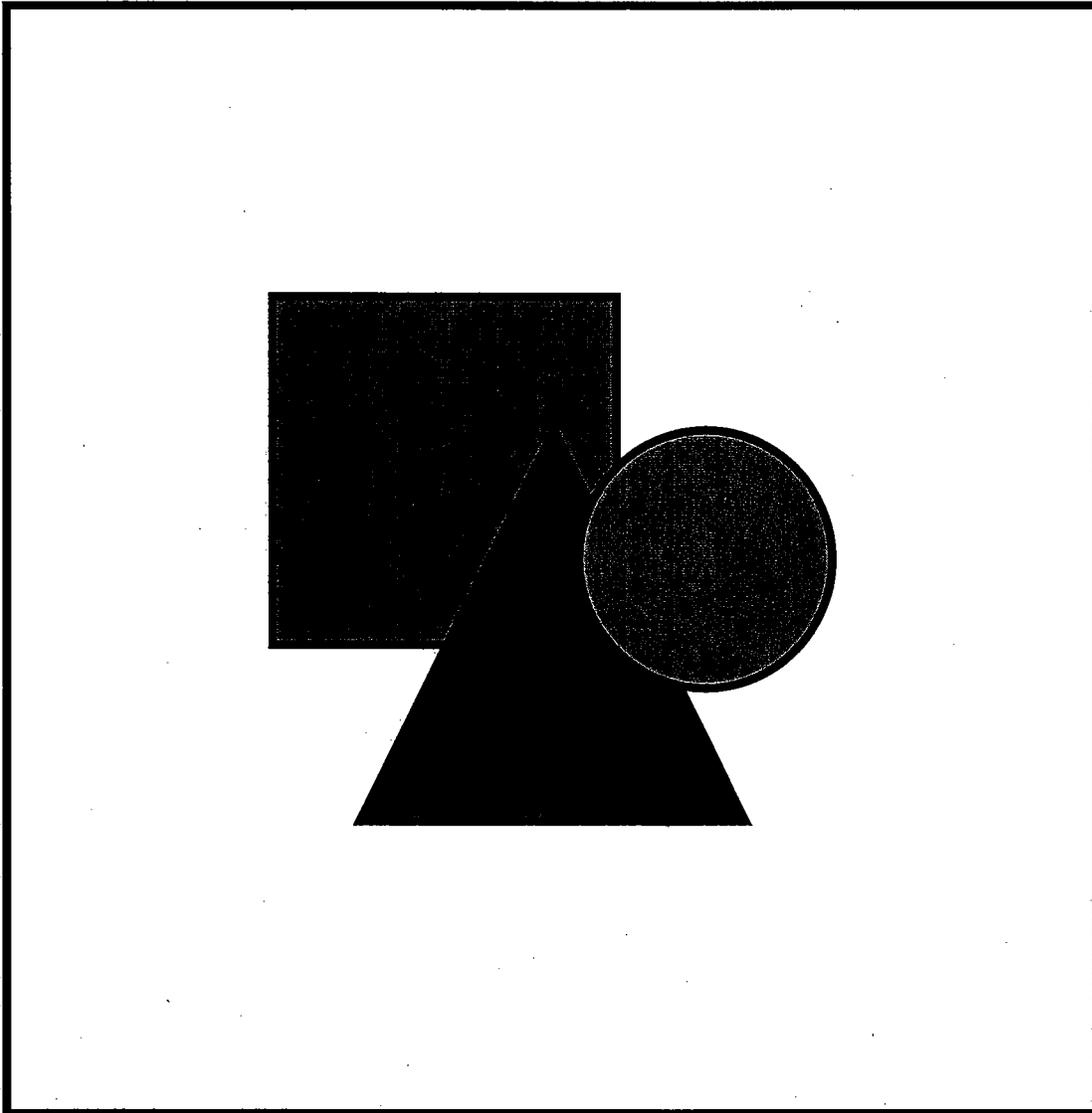
Sponsor's table follows:



Moderate Arterial Desaturation

The percentage of patients experiencing one or more episodes of moderate arterial desaturation and the total duration of episodes were not significantly different between groups. However, the halothane group was found to have significantly more recurrent episodes of moderate desaturation compared to the sevoflurane group (7% versus 4%).

Sponsor's table follows:



Blood Lactate Levels

Following the interim analysis, lactate levels were measured before surgery and pre-bypass. No significant differences between groups was observed.

Interim Analysis

Blinded interim analysis was performed after completion of 91 patients and showed no significant difference between groups in the incidence of the primary outcome variables, CVD and SAD. No p-value adjustment was made for the final analysis p-values.

Renal Assessments

To satisfy the terms of the pediatric written request, evaluation of renal function parameters (blood urea nitrogen (BUN), serum creatinine, and urine output) was done by retrospective review of the patients' medical records.

Mean values for BUN, creatinine, and urine output before surgery and at 24 and 72 hours after surgery were not significantly different between the halothane and sevoflurane groups. Similarly, the mean changes in these parameters from baseline were also not found to be significantly different. However, the individuals with the largest elevations in BUN and creatinine were found in the sevoflurane group. 71 (sevo) and 69 (hal) patients were evaluable for 24-hour changes in BUN; 71 and 68 were evaluable for 24-hour changes in creatinine. 72-hour changes in BUN were evaluable in 46 (sevo) and 42 (hal) patients; 46 and 43 patients were evaluable for 72-hour changes in creatinine. Urine outputs were evaluable in 78 sevoflurane patients and 76 halothane patients at 24 hours post-surgery. At 72 hours, 31 sevoflurane patients and 33 halothane patients had evaluable urine outputs.

The following narratives detail the patients with the largest elevations of BUN and serum creatinine levels coincident with sevoflurane administration:

— is a 5 year old male with previous Blalock-Taussig shunt and bi-directional Glenn procedure. Fontan procedure was performed, during which the patient developed low blood pressure with severe metabolic acidosis. His chest had to be left open. The patient developed multi-organ failure, and BUN/creatinine rose from a baseline of 12/0.4 to a high of 115/3.8 on post-operative day (POD) 3. Daily dialysis was performed, and the patient was transferred to another hospital at the request of the parents on POD 4.

— is a 4.5 year old girl with previous Blalock-Taussig shunt and bi-directional Glenn procedures. The patient underwent atrial septectomy, tricuspid, VSD, and PA repair, and she developed a refractory ventricular arrhythmia postoperatively. She then developed multi-organ failure (renal, hepatic, CNS), and her BUN/creatinine rose from a baseline of 17/0.4 to a high of 98/3.1 on POD 2. She required dialysis, and she subsequently died on POD 5 of cardiac arrest with cerebral edema, herniation, and brain death.

In addition, a 7-month-old male who had a VSD repair under sevoflurane had BUN/creatinine of 48/1.3 on POD 5, up from 21/0.8 on POD 1. Subsequent and preoperative values are not known. A 2-month-old male who underwent ASD/VSD, PDA repair with sevoflurane had BUN/creatinine of 5/1.4 on POD 0, compared to 5/0.3 preoperatively. By POD 2, BUN/creatinine were back to 5/0.2.

Lesser elevations in BUN/creatinine (creatinine \leq 1) were seen in 12 additional patients, of which 9 patients received halothane.

Comments:

Retrospective analysis of BUN, serum creatinine, and urine output was undertaken by chart review. The post-hoc nature of these results, coupled with the incompleteness and lack of uniformity of data points, makes interpretation of the results difficult. In addition, BUN, serum creatinine, and urine output are relatively inaccurate measures of renal function.

Therefore, it is impossible to make definitive conclusions about the effects of sevoflurane versus halothane on renal function in the population tested. Post-operative changes in BUN, creatinine, and urine output were not significantly different between groups; however, the greatest individual elevations in BUN/creatinine were seen in the sevoflurane group. The two patients who required dialysis postoperatively had complicated medical courses leading to renal failure. However, a contributing role of sevoflurane in the development of renal failure can not be ruled out.

SPONSOR'S CONCLUSIONS

Based on the results reported above, the sponsor has made the following conclusions:

DISCUSSION

Several issues relating to study design, execution, and analysis significantly weaken the conclusions that can be drawn from this trial.

1. Blinding: The anesthesiologists were not blinded to the choice of study drug. While this is unlikely to affect the occurrence of events such as bradycardias, desaturations and junctional dysrhythmias, it is quite possible that it would affect the use of pressors. One enrolled patient randomized to halothane was dropped from the study at the investigator's request. This implies that there was the perception by the investigators that sevoflurane is a safer agent for at least some of these patients. Such a perception could certainly influence their use of pressors. Furthermore, a blinded observer was reported to have recorded primary and secondary outcome measures. "Blinding" in this case must be taken with some skepticism for the following reasons:
 - a. During inhalation inductions, it is common for others present in the room to smell the inhalation agent being employed. It is not implausible that this alone would give away the identity of the inhalation agent in use.
 - b. Vaporizers used for delivery of inhalation agents are color-coded. They must also be placed in a specific order relative to one another in the anesthesia circuit based on their relative physical properties. If the observer was in a position where he/she had a good view of the patient, it is likely that the observer would also be able to see what vaporizer was in use.

However, because much of the data collection was automated (hemodynamics, saturations, ECG), the observer probably did not significantly affect the final outcome of this study.

2. Dropouts: One patient was dropped from the study at the investigator's request following randomization to the halothane arm. This was done because the patient was thought to be too "sick" to receive halothane (ventricular bigeminy was noted prior to induction). This raises some concern over the fairness of the recruitment and randomization procedures.
3. Although the groups were well balanced on the whole, and not statistically different, the halothane group had fewer ASA II patients compared to the sevoflurane group (12% versus 23%), and therefore more ASA III/IV patients.
4. Resting values for arterial saturation, blood pressure, and heart rate were to be the lowest values for each parameter based on 3 different estimates: the pre-operative, pre-induction, and nomogram estimates. Therefore, the nomogram estimate constitutes an important component of the determination of resting values, which in turn are critical to the assessment of many of the study's primary and secondary endpoints. Information was requested from the sponsor on the nomogram used for this study. The response consisted of 2 literature articles. One reported on blood pressures in normal healthy children aged 5-16 at their annual doctor's visit. The other reported on pulse and blood pressure measurements on children aged 6 months to 5 years of age, although some values were based on as few as 5 children. Thus, the sponsors have apparently used blood pressure, heart rate, and arterial saturation data from normal healthy children as a basis upon which to make determinations of the occurrence of desaturation, tachycardia, bradycardia, and hypotension in a population of children with multiple forms of severe congenital heart disease. This makes clinical interpretation of the data confusing and difficult. Additionally, the submitted literature indicates some potential weaknesses in the data from which the nomogram was apparently derived.

Of the 180 children in the evaluable population, 136 (76%) of baseline heart rate values and 104 (58%) of baseline mean arterial pressures were from nomogram. In the halothane group, 72% of baseline heart rate values and 55% of baseline mean arterial pressures were derived from nomogram.

5. Analysis:

- An interim analysis was performed without p-value adjustments.
 - Although 15 secondary variables were planned in the protocol, the study report analyzed 18. Lactate levels were added following the interim analysis, but in addition, “emergent drug use” was changed. The original protocol called for analysis of epinephrine or phenylephrine use. The study report looked at 3 different categories: phenylephrine, epinephrine, or ephedrine use; atropine use; and phenylephrine, epinephrine, ephedrine, or atropine use.
 - Many primary and secondary measures were further broken down into multiple subcategories that were not described in the original protocol. These events were analyzed by the percentage of patients who experienced that event, the total duration of episodes, and the distribution of patients by number of episodes. In analyzing so many different variables and sub-variables, the finding of “significance” at the $p \leq 0.05$ level becomes much less meaningful without some adjustment to the significance level.
 - The primary outcome measures were not found to be significantly different between the two treatment groups. 1 _____
-

6. The study report states that “Protocol deviations occurring during the study were not appropriately documented by the investigator; however, it was determined that analyses of the primary and secondary outcome variables were not compromised by this omission.” If protocol deviations were not documented, it should be difficult to assess the impact on the analysis of primary and secondary outcome variables.
7. Pacemaker: Patient 73 in the sevoflurane group was on a pacemaker prior to enrollment. This patient was appropriately excluded from analyses of severe and moderate bradycardia as well as junctional and ventricular dysrhythmias. However, because a pacemaker is likely to offer some protection from hypotension and desaturation, this patient should have probably been excluded from analyses of hypotension, pressor requirements, and desaturations.
8. Other medications: Medications that could affect the occurrence of primary or secondary outcome events, such as midazolam, nipride, albumin, lasix, dopamine and calcium chloride, were not regulated in the protocol. 5% of halothane treated patients received midazolam,

compared to 2% in the sevoflurane group. 10% of halothane patients received calcium chloride, compared to 6% in the sevoflurane group.

10. Renal effects: The largest individual elevations in BUN and serum creatinine postoperatively were seen in patients given sevoflurane. However, the limitations of this retrospective analysis preclude any definitive conclusions about the relative renal effects of halothane versus sevoflurane. This should be regarded as a still-open question that deserves further exploration.

In light of the concerns regarding study execution and analysis, these results should be viewed with some uncertainty. There are trends in the data that

s: _____

t: _____

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/s/

Nancy Chang
2/26/01 01:12:24 PM
MEDICAL OFFICER

you have ok'd this

Bob Rappaport
2/26/01 03:53:51 PM
MEDICAL OFFICER

NDA: # 20478

DOC ID: S-006B2

NAME: Ultane (Sevoflurane) volatile liquid for inhalation

SPONSOR: Abbott Laboratories

SUBMISSION DATE: 3/20/01

REVIEW DATE: 3/24/01

TYPE OF SUBMISSION: Amendment to S-006, updated labeling and safety update

REVIEWER: Nancy Chang, MD

SUMMARY:

The labeling contained in this submission was discussed in a teleconference with the sponsor on 3/24/01. Please refer to the minutes of this meeting and to the medical review of S-006.

The safety review reports adverse drug reactions to sevoflurane in patients under 18 years of age from 5/31/00 through 2/28/01. These cases were collected from the sponsor's post-marketing safety database and the literature. The individual cases are summarized, but copies of the original case reports are not provided. The report is significant for the following labeled adverse events: four cases of malignant hyperthermia and five cases of delirium, agitation, or personality disorder. In addition, 6 reports of convulsions associated with sevoflurane use were described. Convulsions are not currently described in the Ultane label. We have previously noted a number of reports of seizures during our routine post-marketing surveillance, and we are awaiting input from OPDRA prior to initiating an action.

Other described cases report isolated events that are either anticipated events associated with anesthesia and sevoflurane, or events that are difficult to attribute to sevoflurane, due to insufficient information or alternative explanations.

Conclusion:

1. An ongoing discussion of labeling with the sponsor is expected.
2. Final decisions regarding the association of seizures with sevoflurane will await OPDRA input.

Nancy S. Chang, MD
Medical Officer

CC: Division File
Original NDA #20-478
HFD-170 Nancy S. Chang, MD
HFD-170 Lisa Basham

/s/

Nancy Chang
3/22/01 04:46:11 PM
MEDICAL OFFICER

you saw this already - email of 3/22

Bob Rappaport
3/28/01 01:11:20 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-478/S-006

STATISTICAL REVIEW

Statistical Review and Evaluation

PEDIATRIC EXCLUSIVITY DETERMINATION

NDA 20-478/serial no. 6
Name of drug: Ultane (sevoflurane)
Applicant: Abbott
Indication: general anesthesia
Document reviewed: letter 31 May 2000
Project manager: Judit Milstein
Medical officer: Patricia Hartwell, M.D.

Reviewer: Thomas Permutt

FDA issued a written request for pediatric studies of sevoflurane to Abbott 2 March 2000. A comparative study of sevoflurane and halothane with "at least 90 patients per treatment arm" was requested. This sample size was justified as follows: "It is estimated that a minimum of 90 patients will be required in each group to provide an 80% chance of detecting a difference between halothane and sevoflurane in the occurrence of severe arterial desaturation or cardiovascular decompensation, using a significance level of 0.05." The written request was in response to a proposal by Abbott, and the proposed sample size and its justification were taken from Abbott's proposal.

The final study report was submitted 31 May 2000 with a request for pediatric exclusivity. Ninety-one patients were randomized to sevoflurane and 90 to halothane. One patient in each group was withdrawn after randomization but before treatment. The sevoflurane patient was withdrawn because of an equipment failure¹. The patient assigned to halothane was withdrawn because the investigators judged that it might not be safe to treat him with halothane and that sevoflurane should be used instead. This leaves only 89 patients actually treated with halothane, so that some question has arisen as to whether the reported study is literally responsive to the written request.

I believe the study was in this respect precisely responsive to the request and conducted according to best experimental practice. The required number of patients were "studied" in the sense that they were enrolled and followed to endpoint. The withdrawal of the patient from the assigned treatment was appropriate, correctly documented and correctly handled both in the conduct and in the analysis of the study. The patient was not replaced and should not have been replaced: replacement can produce biases whose potential damage to the interpretation of the study far outweighs the benefit of having additional patients. The

¹ Details concerning the withdrawn patients were obtained by Dr. Hartwell in a telephone conference with the applicant.

patient's data were not included even in the "intent-to-treat" analysis, because he did not receive halothane; this exclusion was also correct.

It may also be noted that the figures that went into the computation of sample size are round numbers, and that the statistical information in a group of 89 patients is negligibly different from that in a group of 90 patients. This is always the case, however, and bright lines may need to be drawn anyway. I therefore think it is more important to note that there were in fact 90 patients in the halothane group, as requested. It is normal that not all the patients enrolled would be treated according to the protocol, and not unusual that two patients would not receive study drug at all. The handling of these cases in the conduct and analysis of the study was precisely as I should have recommended. I therefore consider the study to be perfectly responsive to the written request as concerns the sample size.

Thomas Permutt, Ph.D.
Mathematical Statistician (Team Leader)

NDA 20-478/serial no. 6

cc:

HFD-715/Nevius

HFD-170/Milstein, Hartwell, Rappaport, McCormick, Permutt

HFD-170/division file

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-478/S-006

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-478 SUPPL # 006
Trade Name Ultane Generic Name sevoflurane

Applicant Name Abbott HFD- 170

Approval Date March 30, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO / X /

b) Is it an effectiveness supplement? YES / X / NO / ___/

If yes, what type(SE1, SE2, etc.)? SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / ___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / X / NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO / X /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-478 sevoflurane

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly

available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / X /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / X /

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / X /

If yes, explain:

- (c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SEVO-96-412

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / X /

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

! protocol and study were
!
! submitted under the NDA

Investigation #2 ! (20-478)

IND # _____ YES /___/. ! NO /___/ Explain:
!
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ /

NO / X /

If yes, explain: _____

Lisa E. Basham-Cruz
Signature of Preparer
Title: Regulatory Project Manager

4/12/02
Date

Cynthia G. McCormick, M.D.
Signature of Office or Division Director

4/12/02
Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**This is a representation of an electronic record that was signed electronically and
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/s/

Lisa Basham-Cruz
4/12/02 02:03:51 PM

Cynthia McCormick
4/12/02 05:42:01 PM



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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Division Director's Review

DATE: March 30, 2001

FROM: Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: DFS, NDA #20-478 Ultane® (sevoflurane) SE8-006

RE: Basis for Action

This is a supplemental application that provides for changes to the approved Ultane® (sevoflurane) label to include information from a clinical trial of Ultane® in elective cardiovascular surgery in pediatric patients. This 180-patient study comparing Halothane with Ultane® was performed in response to a Pediatric Written Request and has satisfied the terms of that request. As expected, pediatric labeling changes have resulted from this supplement.

Dr. Nancy Chang's clinical review and Dr. Stella Grosser's statistical review have concluded that the prespecified primary outcome measures in this study, of severe arterial desaturation and cardiovascular decompensation were not significantly different between the two treatment arms. Upon subanalysis of the 15 secondary variables, the sponsor was able to detect some differences in overall pressor use, fewer instances of moderate arterial desaturation and moderate bradycardia all favoring sevoflurane. As Dr. Chang has pointed out, these results may also be subject to bias. The specific efficacy claims that the sponsor requested have not been supported and therefore will not be granted.

The supplement was capable of supplying additional safety data about sevoflurane in this clinical setting. The study was limited largely to the cardiovascular system and reports of adverse events. The data provided in the 4-month Safety Update revealed six reports of convulsions, a previously unlabeled adverse event. A careful reanalysis of the postmarketing data was performed by Drs. Chang and Pollack, which revealed additional cases of seizures associated with sevoflurane than had been reported

previously. Since these reports were derived from postmarketing experience in the 7 years since approval no rates could be calculated. While these were largely in pediatric patients there were some adult reports as well. There was one death that could not be directly attributed to sevoflurane. _____

Changes to the package insert have been negotiated.

Action:

Approval of supplement with changes in the package insert.

Cynthia G. McCormick, MD
Director,
Division of Anesthetic, Critical Care and Addiction Drug Products

/s/

Cynthia McCormick
3/30/01 05:56:24 PM
MEDICAL OFFICER

Division of Anesthetic, Critical Care, and Addiction Drug Products

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Application Number: NDA 20-478/SE8-006

Name of Drug: Ultane® (sevoflurane)

Sponsor: Abbott Laboratories

Supplement Number under review:

Package Insert: SE8-006, dated May 31, 2000, amended March 9, 2001, and March 20, 2001 (updated labeling).

RPM: Lisa E. Basham

Date of Review: March 20, 2001

Background and Summary Description:

SE8-006, dated May 5, 2001, received June 1, 2001, provides for changes to the approved labeling to address the use of Ultane® (sevoflurane) in pediatric patients with congenital heart disease. The package insert included in the original submission was not the latest approved label. Therefore, the supplement was amended on March 9, 2001, received March 12, 2001, to provide updated labeling. An additional amendment, dated March 20, received March 21, 2001, incorporated additional safety data derived from a safety update submitted on the same date.

Material Reviewed:

— (SLR-003 approved August 6, 1998), and RPM review, dated December 20, 2000.

SLR-003 C: correspondence, dated October 11, 2000

SE8-006: dated May 31, 2000, amended March 9, and March 20, 2001

Review

Please note that, where appropriate, the sponsor's revisions are indicated by strikeovers and underlined text.

WARNINGS: No changes noted.

PRECAUTIONS: No changes noted.

ADVERSE REACTIONS: Section added between **Adverse Events** and **Laboratory Findings**:

OVERDOSAGE: No changes noted.

DOSAGE AND ADMINISTRATION:

HOW SUPPLIED:

ULTANE (sevoflurane), Volatile Liquid for Inhalation, is packaged in amber colored bottles containing 250 mL sevoflurane, List 4456, NDC # 0074-4456-02 (glass) and NDC # 0074-4456-04 (plastic).

Conclusions:

Labeling changes in the **PHARMACODYNAMICS; Pediatric Anesthesia, CONTRAINDICATIONS, and ADVERSE REACTIONS** sections are subject to

review of SE8-006 by the medical reviewer, with the following note: Under **Adverse Events During Post-Marketing Experience**, the following change should be made:

Labeling changes in all other sections are supported by prior submissions and are acceptable.

Lisa E. Basham/Regulatory Project Manager

Cathie Schumaker/Supervisory Comment/Concurrence

/s/

Lisa Basham
3/22/01 10:03:57 AM
CSO

Cathie Schumaker
3/22/01 04:13:08 PM
CSO

MEMORANDUM OF TELECON

DATE: March 22, 2001

APPLICATION NUMBER: NDA 20-478/S-006, Ultane (sevoflurane)

BETWEEN:

Name: Charles McLeskey, M.D., Sr. Medical Dir., Anesthesia/Pain Management
Letitia Delgado-Herrera, Director of Proprietary Programs
Susan Galvez, Senior Medical Manager
Janet Lim, M.D., Sr. Director, Medical Affairs
Jane Li, M.D., Associate Medical Director
Susan Olinger, Director of Proprietary Programs
Mike Sliwoski, Associate Director, Perioperative Programs
Phone: 1-888-330-4559
Representing: Abbott Laboratories

AND

Name: Cynthia G. McCormick, M.D., Director
Bob Rappaport, M.D., Deputy Director
Nancy Chang, M.D., Medical Reviewer
Lisa E. Basham, Regulatory Project Manager

Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Discussion of labeling changes related to pediatric supplement 006

In a telephone conference on March 22, 2001, initiated by the Agency, labeling changes and the clinical study were discussed. The sponsor was informed that the proposed claims o. _____

_____ An important reservation in concurring with the sponsor's conclusions relates to the reliance on secondary endpoints, when primary endpoints were not found to be statistically significant. Fifteen secondary endpoints were pre-specified, and these were further broken down into many subcategories, making a determination of statistical significance doubtful. The following Agency proposed changes were communicated:

1. Under **Pediatric Anesthesia**, the following text is recommended to replace the sponsor's proposed changes:

Sevoflurane (n=91) was compared to halothane (n=89) in a single-center study for elective repair or palliation of congenital heart disease. The patients ranged in age from 9 days to 11.8 years with an ASA physical status of II, III, and IV (18%, 68%, and 13% respectively). No significant differences were demonstrated between treatment groups with respect to the primary outcome measures: cardiovascular

decompensation and severe arterial desaturation. Adverse event data was limited to the study outcome variables collected during surgery and before institution of cardiopulmonary bypass.

2. The **CONTRAINDICATIONS** section should read as follows:

Sevoflurane can cause malignant hyperthermia. It should not be used in patients with known sensitivity to sevoflurane or other halogenated agents, nor in patients with known or suspected susceptibility to malignant hyperthermia.

3. A **Pediatric Use** section should be added according to 21 CFR 201.57(f)(9). The sponsor will propose the language and fax the proposal to the Agency for discussion.
4. The Agency is awaiting a review from the Office of Post-Marketing Drug Risk Assessment (OPDRA) on the occurrence of seizures in patients exposed to sevoflurane. The following language, however, is proposed for the section **Adverse Events During Post-Marketing Experience**, with the understanding that additional changes may be forthcoming upon receipt of the review.

Rare cases of malignant hyperthermia have been reported (see **CONTRAINDICATIONS** and **WARNINGS**).

Additional discussion involved the use of nomogram data to establish baseline hemodynamics in a trial evaluating deviation from baseline as a primary endpoint. Dr. Chang stated that this makes interpretation of the data problematic in that the baseline values are of questionable validity. The sponsor responded by stating that the baselines used were actual patient baselines and will forward this clarification to the Agency. Dr. Chang went on to state that other medications not pre-specified and accounted for in the analysis could have affected the outcome measures of the study. She suggested that it would be better in the future to pre-specify these medications, or at least include their use in the analysis of the study.

This memo will be forwarded to the sponsor via fax. Proposed labeling for the **Pediatric Use** section of the labeling will be submitted to the Agency via fax for review.

Lisa E. Basham
Regulatory Project Manager

Cynthia G. McCormick, M.D.
Director

/s/

Lisa Basham
3/22/01 05:15:34 PM
CSO

Cynthia McCormick
3/22/01 05:24:31 PM
MEDICAL OFFICER